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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Philip H. Sheridan, M.D.
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Established Name	Repository Corticotropin
(Proposed) Trade Name	Acthar Gel
Applicant	Questcor Pharmaceuticals
Formulation(s)	For Intramuscular Injection
Dosing Regimen	BID
Indication(s)	Infantile Spasms
Intended Population(s)	Pediatric

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval is recommended for the treatment of infantile spasms, (b) (4) . A REMS and changes to proposed labeling are needed as discussed in sections 9.2 and 9.3 of this review.

The efficacy and safety study data, although strongly suggestive of efficacy and relative safety, do not meet the usual Agency standard for NDA approval as discussed in this review. However, given the inherent difficulties of further studying the efficacy and safety of Acthar Gel therapy for infantile spasms and the continued off-label use of Acthar Gel for this indication, the appropriateness of approving Acthar Gel for the treatment of infantile spasms on the basis of the data presented was reviewed by the Peripheral and Central Nervous System Drugs Advisory Committee on May 6, 2010 as discussed in section 9.3 of this review.

1.2 Risk Benefit Assessment

The single pivotal study (CSR 222017-01 by Baram) is strongly suggestive but not definitive (by usual Agency standards) for establishing efficacy in eliminating the spasms. Two controlled studies by Hrachovy (CSR 222017-05 and CSR 222017-04) are also consistent with efficacy but are supportive data rather than pivotal efficacy trials. As discussed in detail in this review, all three studies have significant flaws in design and analysis. The usual standard for NDA approval is not met. The safety data is extensive but largely retrospective.

The argument for approval based on the submitted data could be made as follows. Although vigabatrin was recently approved for the treatment of infantile spasms in the United States (after recommendation by an advisory committee which accepted less than the usual standard of evidence for efficacy and safety), vigabatrin raises significant safety concerns (visual field deficits and intramyelinic edema) that are not yet adequately defined and/or detectable by monitoring and which require an extensive REMS. Most American patients with infantile spasms are currently treated off-label with Acthar Gel even though there is considerable variability in the dosage and duration of treatment. As discussed in this review and in a recent AAN review cited in this submission (MacKay, 2004), available efficacy and safety data suggest that the proposed dosage (high dosage, short duration) is probably effective and relatively safe in controlling spasms (although its effect on long-term neurodevelopmental status is not

established). Approval would establish reasonable dosage and duration guidelines for prescribers.

The adverse effects documented in these studies are consistent, readily recognizable, manageable, and usually reversible after the relatively short treatment period is completed.

The argument against such an approval in the absence of the usual criteria for efficacy is that the usual standards for efficacy should be met. A proposal to market Acthar Gel to treat infantile spasms would be more compelling if, in addition to stopping spasms, there was evidence demonstrating or strongly suggesting that stopping the spasms improves the long-term neurodevelopmental prognosis for the affected infants. Although it may be that long-term developmental prognosis improves if spasms can be stopped early-on infantile spasms, the evidence is not convincing for either Acthar Gel or vigabatrin.

Infantile spasms is a catastrophic epileptic syndrome that would justify use of a probably effective therapy even given some uncertainty over efficacy, safety, and optimal dosage. As discussed in section 9.3 of this review, the advisory committee supported the approval of Acthar Gel for the treatment of infantile spasms with recommendations for precautions and future long-term studies (as dsicussed in section 9.3 of this review).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

REMS to provide a MedGuide for the infantile spasm indication.

Revision of labeling as discussed in section 9.2 of this review

1.4 Recommendations for Postmarket Requirements and Commitments

None. See discussion in section 9.3 of this review.

2 Introduction and Regulatory Background

2.1 Product Information

See currently approved label.

2.2 Tables of Currently Available Treatments for Proposed Indications

Vigabatrin (Sabril) was recently approved for treatment of infantile spasms.

2.3 Availability of Proposed Active Ingredient in the United States

Currently approved and marketed for other indications.

2.4 Important Safety Issues with Consideration to Related Drugs

The primary safety issues of Acthar Gel are related to its stimulation of endogenous steroid production. The adverse effect profile is thus similar to that of steroid medications including irritability, Cushingoid appearance, hypertension, and decreased resistance to infection;

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Acthar Gel was approved in 1952 and was successively owned by several companies including Armour Pharmaceutical Company, Rhone-Poulenc Rorer, and Aventis. Aventis was formed by the merger of Rhone-Poulenc Rorer with Hoechst AG.

In 2001, Questcor purchased the marketing rights to Acthar from Aventis. Since that time, with active collaboration with the Food and Drug Administration (FDA), Questcor has been working to submit a Supplemental New Drug Application (sNDA) that would support the approval of Acthar for the treatment of patients with infantile spasm (IS).

Questcor received a Complete Response letter to its sNDA submission with specific deficiencies in May 2007. In a subsequent Type C Meeting with FDA in November 2007 (09 November 2007 Type C Meeting Minutes, correspondence), Questcor was encouraged to do the following, where possible:
1. Obtain the source data from the 5 published, randomized control studies where Acthar was evaluated for the treatment of patients with IS and perform independent analyses of the data (Askalan 2003, Baram 1996; Dreifuss 1986; Hrachovy 1994; Hrachovy 1983); 2. Obtain source data from hospitals that had treated patients in the last 10 years and then to perform its own independent safety analyses of these data.
3. Provide FDA with safety on enough IS patients treated with Acthar to define the safety profile in these patients and to support that the benefit outweighs the risk.

Following this meeting, Questcor attempted to obtain data from the 5 RCTs, and was successful in obtaining data from 3 of those 5 studies (Baram 1996, Hrachovy 1994, Hrachovy 1983). Data for the other 2 RCTs were no longer available due to the age of

those studies. In addition, Questcor obtained data from a safety study conducted in 2007 (Partikian 2007) and also conducted its own retrospective chart review protocol to obtain source safety data from IS patients treated at 4 hospitals.

2.6 Other Relevant Background Information

Not applicable

3 Submission Quality and Integrity

3.1 Submission Quality and Integrity

As discussed in detail in this review, the three studies presented in support of efficacy and the four studies presented in suport of safety do not meet usual Agency standards for approval. The Sponsor has shown due diligence in obtaining the most complete data available and in presenting them with scientific integrity.

Efficacy Data Quality:

Most NDA submissions provide efficacy data collected prospectively using prespecified protocol and comprehensive patient data collection forms from a double blinded randomized study of the NDA study drug versus a control (placebo or active control). Because the studies supporting this NDA were done as small academic studies and not intended to support an NDA submission, this quality of efficacy data is not available. Furthermore, there was no formal follow-on protocol after the pivotal efficacy study or after the supportive efficacy study that could provide a reliable relapse rate for all responders over a 6 month or greater time period. Longer-term data concerning neurodevelopment or the later appearance of other forms of epilepsy among the responders are not available.

A complete prospective protocol, comprehensive patient data collection forms, and prespecified statistical analysis plan were not available.

Safety Data Quality:

Most NDA submissions provide safety data collected prospectively using prespecified protocol and comprehensive patient data collection forms from a double blinded randomized study of the NDA study drug versus a control (placebo or active control). Because the studies supporting this NDA were done as academic studies and not intended to support an NDA submission, this quality of safety data is not available. The

safety data presented was compiled retrospectively in an unblinded fashion from the charts of patients who had participated in academic randomized clinical studies or who were treated for infantile spasms independent of a randomized trial at an academic center. The data available in the charts was not collected according to predetermined prospective protocol and patient data collection forms. Thus, the data is prone to be incomplete. The patient charts from the pivotal efficacy study were not available to the Sponsor so this study did not directly contribute any safety data.

This safety information is supplemented by adverse event reports submitted to the Sponsor and by a survey of adverse events attributed to Acthar Gel in the published literature. These are useful in screening for adverse effects observed in the larger treatment population (beyond the safety studies used in this submission) that were not identified in the relatively small number of study patients receiving Acthar Gel (319 patients in 3 safety studies). However, the likelihood of an observed adverse effect being reported from this larger population is unknown making the numerator of an estimated incidence of an observed adverse effect uncertain. Furthermore, the size of this larger treatment population is not known so there is also no denominator for estimating incidence of adverse effects observed.

3.2 Compliance with Good Clinical Practices

Adequate

3.3 Financial Disclosures

Questcor submitted the following statement with Form FDA-3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) dated 8/31/09 regarding the three efficacy studies and one of the safety studies (Partikian 2007 or CSR 222017-02):

Attachment to Form FDA-3454

Investigators and Subinvestigators with No Financial Arrangement with Sponsor

(b) (4)

[redacted]

As the applicant who is submitting studies sponsored by a firm or party other than the applicant, Questcor certifies that based on information obtained from participating clinical investigators, the listed clinical investigators above did not participate in any financial arrangement with Questcor. Due to the literature source of the above studies, Questcor has listed the primary author as the principal investigator and the co-authors of the publications as the subinvestigators.

With respect to Safety Study QSC007-ACT-002, Questcor submitted the following list with Form FDA-3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) dated 8/31/09

Attachment to Form FDA-3454

Investigators and Subinvestigators with No Financial Arrangement with Sponsor

(b) (6)

(b) (6) and (b) (6) are identified as subinvestigators for Study (b) (4) and also as having a paid consulting arrangement with Questcor. My review of their stated roles in the study does not suggest the likelihood of the introduction of bias to this study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Not applicable

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Efficacy Studies	Title
CSR 222017-01	Pivotal Efficacy Study: High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms: A Prospective, Randomized, Blinded Study (Baram, 1996)
CSR 222017-05	Supportive Efficacy Study: High-dose, Long-duration versus Low-dose, Short-duration Corticotropin Therapy for Infantile Spasms (Hrachovy, 1994)
CSR 222017-04	Additional Data for Efficacy: High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms, A Prospective, Randomized, Blinded Study (Hrachovy, 1983)

Safety Studies	Description	Number of Acthar Gel-treated patients contributed to Integrated Safety Tables
CSR 222017-02	Partikian and Mitchell retrospective chart review	84
CSR QSC007-ACT-002	Questcor retrospective chart review at 4 sites	178
CSR 222017-05	Hrachovy 1994 Study of Acthar Gel High vs Low Dose (charts reviewed retrospectively for safety data)	57
CSR 222017-04	Hrachovy 1983 study of ACTH vs Prednisone (patients on Acthar gel not identifiable in retrospective chart review)	None
Total Patients in Integrated Safety Tables	See section 7.2.1 of this review	**319**

5.2 Review Strategy

I have reviewed the individual clinical study reports and the integrated summaries of efficacy and safety for the efficacy and safety studies. I have also reviewed the published articles from the three efficacy studies and from the Partikian safety study, and I have compared them to the corresponding clinical study reports.

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 presented as the pivotal efficacy study.

Questcor also obtained source efficacy data from the 2 additional RCTs conducted and published by Dr. Hrachovy and colleagues (Hrachovy 1994, Hrachovy 1983). Questcor's independent 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.

All three studies assessed the efficacy of Acthar Gel by the combined primary endpoint of cessation of spasms (determined by video EEG sessions) and the elimination of the hypsarrhythmia.

The safety data submitted in this Complete Response from the independent analyses of the data obtained in studies conducted by Drs. Partikian and Mitchell (CSR 222017-02) which presumably included safety data from CSR 222017-01 not otherwise available, the Questcor Retrospective Study (CSR QSC007-ACT-002), and the studies conducted by Hrachovy and colleagues (CSR 222017-05 and CSR 222017-04), together with the data in the Questcor postmarketing surveillance safety database and the published literature

5.3 Discussion of Individual Studies/Clinical Trials

The Sponsor presents three individual studies in support of efficacy in this NDA submission:

Pivotal Study for Efficacy CSR 222017-01 (Baram, 1996)

The pivotal study was entitled, "High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms: A Prospective, Randomized, Blinded Study". It compared Acthar 150

U/m2/day administered as 75 U/m2/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.

The patients were assessed for both the elimination of clinical spasms as well as a remission of hypsarrhythmic EEG pattern characteristically seen in these patients.

Reviewer's Note:
This combined endpoint (elimination of spasms and of hypsarrhythmia) is generally recognized as the most clinically meaningful endpoint for efficacy studies of infantile spasms. Unlike the efficacy success of treatments of other seizure types where reduced seizure frequency is significant, success for efficacy studies of infantile spasms is an "all-or-none" phenomenon.

The use of video-EEG for assessment of spasms elimination and the elimination of hypsarrhythmia is also essential to a good infantile spasms study. Even experienced clinicians may miss subtle spasms (undercount) or mistake a nonepileptic infantile movement for a spasm (overcount) without a simultaneous EEG tracing for detection or confirmation. Video EEG also allows for a blinded EEG interpreter who does not know to which arm of the study an infant is assigned to determine if the infant's response satisfies the primary endpoint.

This study is considered single blind because the infants were not subjected to a "double-dummy" study where twice-daily sham injections would be given to infants randomized to oral prednisone. However, given that an infant would not be expected to associate one treatment over the other with likely improvement in its condition (or even associte the experience of being treated with any expected benefit) and that the endpoint is objective rather than subjective, it is unlikely that a placebo response affected the outcome. Thus, the study almost can be considered "double-blind".

Dr. Baram and her colleagues had previously published the study results from their analyses of the data (Baram 1996). Questcor obtained the primary efficacy data from the investigators and, with the investigators' permission, Questcor performed an independent analysis for submission in this sNDA; these analyses are presented in CSR 222017-01.

Reviewer Note:

The data available from Dr. Baram was largely limited to her published article (1996) and her spreadsheet of patients. Regrettably, the safety data was not available to Questcor. It is presumed that the 15 patients initially randomized to Acthar Gel and the 9 patients who crossed over to Acthar Gel after initially being randomized to prednisone are included in the patients who were retrospectively

studied by Partikian (See section 7.1.1 of this review). However, none of the patients are definitely identifiable as being from the Baram study.

Design: Patients eligible for enrollment into this study were diagnosed with clinical IS, defined according to Jeavons (1964). An infant previously treated with any steroid or Acthar treatment was not eligible for the study. Informed consent was obtained from each patient's parent or guardian. 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 by a blinded EEG interpreter. Video-EEG monitoring was performed for a minimum of 4 hours and, optimally, for 24 hours, always including a full sleep wake cycle.

Reviewer Note:
It is important that at least one full sleep-wake cycle be observed since the incidence of infantile spasms varies during the cycle. It would be cleaner if all infants had a 24 hour post-treatment video EEG. From available data, It cannot be determined an equal number of the less than 24 hour video EEG sessions occurred in each arm of the study. However, given the "all-or-none" nature of a positive response to infantile spasm therapy, this flaw is probably less significant than it might be in a study of another seizure type.

Adverse events such as hypertension and hyperglycemia were monitored; urine specimens were checked for glucose throughout the duration of treatment, and blood pressure was measured biweekly. The safety results were not included in the published article (Baram, 1996) and were not available for Questcor to include in the clinical study report.

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. Patients with persistent spasms or hypsarrhythmia after initial treatment were offered the alternative treatment.

Video-EEG was used to establish response to treatment. For a patient to be considered an Overall Responder to treatment, both of the following had to occur: remission of clinical spasms and a resolution of the characteristic pattern of hypsarrhythmia on EEG. Electrographic response consisted of resolution of the hypsarrhythmic pattern on both

sleep and wake EEG. The emergence of background slowing or other epileptiform patterns was considered a positive response

Efficacy Findings

Results: Thirty-six (36) patients met clinical and EEG criteria for entry into the study. Two (2) were ineligible for treatment, 1 had severe hypertension and 1 experienced resolution of spasms after shunt placement. Thirty-four (34) patients were, therefore, eligible to enroll in the study.

Twenty-nine (29) of the 34 eligible infants with clinical IS were enrolled in the study; the 5 who were not enrolled were due to parental refusal (2), unavailability of legal guardian (2), and other issues (1).

Fifteen (15) patients were randomized to Acthar and 14 patients were randomized to prednisone. Twenty-five (25) patients (25/29, 86.2%) had symptomatic etiology of IS and 4 patients (4/29, 13.8%) had cryptogenic etiology of IS. No stratification was done prior to randomization, but 2 cryptogenic patients were randomized to each arm.

Reviewer Note:
The older medical literature suggests that cryptogenic patients may respond more often than symptomatic patients. The published article (Baram, 1996) notes that, given modern neuroimaging and other diagnostic testing, the cryptogenic category is smaller than in older reports. In this small study, there was no significant difference in response between cryptogenic and symptomatic patients.

The Questcor analysis of the efficacy data of CSR 222017-01 demonstrated the following:

- The combined clinical endpoint of spasm cessation combined with cessation of the hypsarrhythmic EEG indicated greater efficacy of Acthar (13/15, 86.7%) compared to prednisone (4/14, 28.6%), P=0.0015.
- The differences between Acthar and prednisone for the separate EEG and clinical response of spasm cessation were statistically significant (P=0.0015 and P=0.0003, respectively) favoring the Acthar treatment group. Electroencephalogram response was 86.7% for Acthar and 28.6% for prednisone. Corresponding clinical response rates for spasm cessation were 93.3% and 28.6%, respectively.
- Age distributions appeared to be slightly different between the treatment groups, but these differences were not statistically significant. `

- Adjusting for age group the secondary analyses confirmed that differences between Acthar and prednisone for the combined clinical endpoint and for the separate EEG and clinical spasms responses remained statistically significant (P<0.01, for any age grouping).
- One (1) of 2 patients (1/2, 50%) crossed-over to prednisone responded by both EEG and clinical criteria. Seven (7) of 8 patients (7/8, 87.5%) with data available documenting cross-over to Acthar responded by both EEG and clinical spasm criteria.

Reviewer Note: The published article indicates that 2 patients relapsed of the 14 responding to ACTHAR originally (15% rate). The period of follow-up is not specified. When asked about relapse data, the Sponsor on March 26, 2010 said they had no further information. Further discussion of relapse data is summarized in section 6.1.9 of this review.

Questcor Conclusions: This study demonstrated that Acthar 150 U/m2/day administered as 75 U/m2/bid IM was superior to prednisone 1 mg/kg/bid PO for elimination of clinical spasms and hypsarrhythmia in patients with IS using a 2-week high-dose regimen with a 2-week taper. This Acthar regimen was superior to prednisone when analyzing the overall response endpoint (combined measure of cessation of spasms and eliminating the hypsarrhythmia on EEG) (the more definitive measure of treatment success) as well as in the individual measurements of spasm cessation and elimination of the hypsarrhythmic EEG pattern.

Reviewer Note: All but one of the patients who responded with cessation of spasms also showed disappearance of hypsarrhythmia. The fact that this one patient was on Acthar Gel rather than prednisone is not likely to be significant since there were many more patients with cessation of spasms on Acthar gel (14/15) than on prednisone (4/14).

Supportive Efficacy Study: CSR 222017-05 (Hrachovy 1994)

The supportive efficacy study CSR 222017-05 was entitled, “High-dose, Long-duration versus Low-dose, Short-duration Corticotropin Therapy for Infantile Spasms,” a prospective, controlled, randomized, single-blind study that compared an Acthar high-dose regimen to Acthar low-dose regimen in patients with IS.

The Acthar high-dose regimen consisted of Acthar given at a dose of 150 U/m2/day as a single (150 U/m2/QD) IM dose for 3 weeks followed by a 9-week taper; the Acthar low-dose regimen consisted of Acthar 20 U/day (20 U/QD) as a single IM dose for 2

weeks followed by a 2-week taper in responders or a dose escalation to 30 U/QD IM in nonresponders.
The principal investigator, Dr. Hrachovy, and his colleagues had previously published the study results from their analyses of the data (Hrachovy 1994). Questcor obtained the primary efficacy data from the investigators, and with the investigators' permission, Questcor performed an independent analysis for submission in this sNDA; these analyses are presented in CSR 222017-05.

Reviewer Note:
Unfortunately, although the "high dose" of 150 U/m2/day is the same total daily dose used in the pivotal study (CSR 222017-01, Baram), this "supportive efficacy study" gave the injection once daily rather than dividing the injection BID. The BID dosage is believed to increase the cortisol response which may be related to the mechanism of action for causing cessation of spasms. Also, the high dose is given for 3 weeks and tapered for 9 weeks but the CSR 222017-01 pivotal study gave the high dose for 2 weeks and tapered for 2 weeks. Furthermore, the different timing of the EEG between the two arms of the study makes this study difficult to interpret.

Study Design: Patients enrolled in the study were diagnosed with IS defined by both the presence of clinical spasms and a hypsarrhythmic EEG pattern. All study participants were under the age of 4 years, had onset of spasms prior to the age of 12 months, and continued to have spasms at the time of entry into the study. Patients who had previously received ACTH or corticosteroid therapy for their spasms were not eligible for the study.

Informed consent was obtained from each patient's parent or guardian. Prior to the initiation of treatment, patients were monitored using a video-EEG for up to 24 hours in order to confirm the presence of IS and to establish a baseline seizure frequency. Patients were monitored with video-EEGs 2 to 3 times during the treatment period; the treatment period was 12 weeks for the high-dose and 6 weeks for low-dose. As per the study protocol, the 2 dosing groups had different schedules as to when the post-Acthar EEGs were to be performed. The patients randomly assigned to the Acthar low-dose group were scheduled to have their first post-Acthar EEG performed 2 weeks after the start of treatment, whereas patients in the Acthar high-dose group did not have their first post-Acthar EEG performed until after the Acthar was tapered to zero, a full 12 weeks after the initiation of therapy and 9 weeks after the maintenance dose of 150 U/m2/QD had been administered. Patients were evaluated throughout the study for spasm cessation and safety.

Treatment Protocol: Eligible patients were first stratified as having either cryptogenic or symptomatic IS and then randomized to receive treatment with either high-dose Acthar (150 U/m2/QD IM for 3 weeks, followed by 80 U/m2/QD IM for 2 weeks, then 80 U/m2/every other day [QOD] IM for 3 weeks, then 50 U/m2/qod IM for 1 week, and then

Acthar was tapered to zero over 3 weeks) or Acthar low-dose (20 U/QD IM for 2 weeks). Nonresponders to the high-dose Acthar regimen were treated with prednisone 2 mg/kg/day PO for 4 to 6 weeks, and then followed in a routine clinical manner. Nonresponders to low-dose Acthar had their Acthar increased to 30 U/QD for an additional 4 weeks followed by a taper to zero over a 2-week period.

Data Methods: Procedures used to collect, to analyze, and to ensure the integrity of study data are provided in the final study report (see CSR 222017-05).

Efficacy Measures: 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. 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.

Reviewer Note:
The stratification of cryptogenic vs. symptomatic IS is a good feature of this study which the pivotal study (CSR 222017-01, Baram) did not have. Some reports in the literature suggest that infants with cryptogenic IS have a better initial response overall prognosis.

The length of the video EEG sessions varied. The sponsor does not have records of how long each session was or whether one arm of the study might have averaged longer sessions than the other arm.

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

- Modified Intent-to-Treat Population: The modified Intent-to-treat (mITT)Population, the primary efficacy population, included all patients who were randomized, received ≥ 1 dose of Acthar study medication, and had sufficient data to evaluate the Overall Response (see CSR 222017-05, Section 9.8.8.1).

- Intent-to-Treat Population: The Intent-to-treat (ITT) Population included all patients randomized to treatment. A sensitivity analysis of treatment efficacy was performed using the ITT Population (see CSR 222017-05, Section 9.8.3.2).

- Spasms Population: The Spasms Population included all patients with sufficient data to evaluate the Spasm Control Response.

- Completed Patients Population: The Completed Patients Population included all patients in the study who completed the treatment with Acthar as designed by the

protocol (i.e., were not prematurely withdrawn from the study), and were judged to have completed the protocol by the investigator.

The analysis of treatment response was performed in each of the 4 efficacy populations for each of the 3 responder groups:

- Overall Responders,
- Spasm Control Responders, and
- Hypsarrhythmic EEG Pattern Responders.

Each patient was classified as a Responder or Nonresponder for the determination of Overall Response (i.e., spasm cessation combined with resolution of the hypsarrhythmic EEG pattern), as well as for the determination of Spasm Control Response alone and Hypsarrhythmic EEG Pattern Response alone based on data collected to the Treatment Response case report form page as explained below:

- Overall Response: Overall Responders in this study included all patients with both cessation of spasms and resolution of the hypsarrhythmic EEG pattern at any time during the study.
- Spasm Control Response: Spasm Control Responders included all patients with cessation of spasms at any time during the study. Patients were evaluated for spasms through the treatment and follow-up periods. For the purpose of this analysis, Spasm Control Responders included all patients with cessation of spasms at any time during the treatment or follow-up periods identified by clinical assessment and/or parental reports that were recorded in the patient charts. Any patient noted to have cessation of spasm with who subsequently was observed to have spasms would be considered to have relapsed.

- Hypsarrhythmic EEG Pattern Response: Hypsarrhythmic EEG Pattern Responders included all patients with resolution of hypsarrhythmia as assessed by any post-treatment EEG at any time during the study. Serial long-term EEG and/or video monitoring studies (up to 24 hours) were used to determine the EEG response. If a patient had resolution of hypsarrhythmia on a post-treatment EEG but a later post –treatment EEG showed hypsarrhythmia, that patient would be considered relapsed.

The analysis of relapse was only performed in the Overall Responders in the mITT Population. A relapsed patient was defined as any patient in the mITT Population who, first, met the Overall Responder definition and then had 1 or both of the following conditions occur: 1) the patient demonstrated continued spasms or reduction of spasms following a noted cessation of spasms, or 2) the patient demonstrated any type of hypsarrhythmia on any EEG subsequent to an EEG that showed resolution of hypsarrhythmia.

For the ITT Population only, a sensitivity analysis was performed by applying the following "worst case scenario" definitions to patients with missing data in order to classify them as either Responders or Nonresponders for all 3 endpoints: the Spasm Control Response, the Hypsarrhythmia EEG Pattern Response, and then, by definition, the Overall Response, as follows:

- If a patient assigned to the Acthar low-dose group was not assessed for spasms cessation, then the patient was counted as a Spasm Control Responder.
- If a patient assigned to the Acthar low-dose group was not assessed for resolution of hypsarrhythmic EEG, then the patient was counted as a Hypsarrhythmic EEG Pattern Responder.
- If a patient assigned to the Acthar high-dose group was not assessed for spasms cessation, then the patient was counted as a Nonresponder for the Spasm Control Response.
- If a patient assigned to the Acthar high-dose group was not assessed for resolution of hypsarrhythmic EEG, then the patient was counted as a Nonresponder for Hypsarrhythmic EEG Pattern Response.

Results: The study enrolled 59 patients (30 high-dose, 29 low-dose). Nine patients (4 in the high-dose group, 5 in the low-dose group) did not complete the treatment protocol. Dr. Hrachovy was able to provide charts from 58 patients of the study patients: 50 who completed the study protocol and 8 of the 9 patients who prematurely withdrew from the study. The chart for the remaining patient was not able to be located.

Table 1.1 is a summary of the available dose record (exposure) data, efficacy data, and analysis populations by treatment group.

Table 1.1 Dose Record Data, Efficacy Data, and Analysis Populations by Treatment Group

	Acthar High Dose[a] n=30	Acthar Low Dose[b] n=29	Acthar All Patients N=59
Populations for Efficacy 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)

a. Acthar High Dose: 150 U/m²/qd for 3 weeks, then 80 U/m²/qd for 2 weeks, then 80 U/m²/qod for 3 weeks, then 50 U/m² qod for 1 week, and then tapered to 0 U/qd over 3 weeks.

b. Acthar Low Dose: 20 U/qd for 2 weeks, then the dose was escalated or tapered based on response.

The median age of onset of spasms of all patients in the mITT Population was 6.62 months (range: 1.9 to 28.2 months). The median age of all patients was 6.7 months (range: 2 to 28 months) at start of treatment. The median lag time for all patients from date of diagnosis of IS to start of treatment was 0.1 month (range: 0 to 2 months). The median age of onset of spasms, the median age at start of treatment, and the median lag time to start of treatment was similar in the Acthar high-dose and the Acthar low-dose groups. More patients were male (31/51, 60.8%) than female (20/51, 39.2%); the Acthar low-dose group had a higher proportion of male patients (70.4%) than did the Acthar high-dose group (50.0%). The majority of patients had symptomatic etiology of IS (35/51, 68.6%). Consistent with a stratified design, the distribution of symptomatic and cryptogenic etiology of IS was similar in the Acthar high-dose (70.8% and 29.2%) and Acthar low-dose (66.7% and 33.3%) groups.

Table 1.2 is a summary overview of the primary, secondary, and confirmatory analyses.

Table 1.2 Summary Overview of Overall Response, Spasm Control Response, and Hypsarrhythmic EEG Pattern Response by Treatment Group (Each Efficacy Population)

Populations	Acthar Treatment[a,b]	N	Overall Response	Spasm Control Response	Hypsarrhythmic EEG Pattern Response
mITT Population	High Dose	24	*P*=0.2768	*P*=0.0329	*P*=0.2686
	Low Dose	27			
ITT Population[c]	High Dose	30	*P*=0.9443[d]	*P*=0.0691	*P*=0.5209[d]
	Low Dose	29			
Spasms Population	High Dose	28	*P*=0.6363	*P*=0.0126	*P*=0.6580
	Low Dose	27			
Completed Patients Population	High Dose	26	*P*=0.8225	*P*=0.0782[c]	*P*=0.8349
	Low Dose	24			

a. Acthar High Dose: 150 U/m²/qd for 3 weeks, then 80 U/m²/qd for 2 weeks, then 80 U/m²/qod for 3 weeks, then 50 U/m²/qod for 1 week, and then tapered to 0 U/qd over 3 weeks.

b. Acthar Low Dose: 20 U/qd for 2 weeks, then the dose was escalated or tapered based on response.

c. Sensitivity analysis, data imputed to favor Acthar Low Dose.

d. Mantel-Haenszel test was used to compare response rates between treatments, stratified on etiology. All contrasts showed numerically higher response rate for Acthar high-dose compared to Acthar low-dose except as noted.

Reviewer Note:

The records from this study do not indicate how many of the "low dose" arm patients were increased from 20 U QD to 30 U QD during the treatment period. The "High Dose" arm was given 150 U/m2/day QD which for most patients would be about 40 U QD.

The Questcor analyses of the efficacy data of CSR 222017-05 was as follows:

- In the mITT Population (the primary efficacy population), the Overall Response was similar in the Acthar high-dose (15/24, 62.5%) and the Acthar low-dose (13/27, 48.1%) groups, P=0.2768. However, the Spasm Control Response to treatment did demonstrate statistical significance: this response was greater in the Acthar high-dose group (19/24, 79.2%) than in the Acthar low-dose group (14/27, 51.9%), P=0.0329. The Hypsarrhythmic EEG Pattern Response was similar between the 2 treatment groups: Acthar high-dose (16/24, 66.7%) and the Acthar low-dose (14/27, 51.9%), P=0.2686.

- In the Spasms Population, the Spasm Control Response endpoint demonstrated statistical significance in that there were higher rates of response in the Acthar high-dose group (23/28, 82.1%) compared to the Acthar low-dose group (14/27, 51.9%), P=0.0126.

- A trend in the Spasm Control Response favoring the Acthar high-dose group was observed in both the ITT and Completed Patients Populations. The ITT sensitivity analysis, which used data imputation biased in favor of the Acthar low-dose group, showed a trend towards higher Spasm Control Response rates in the Acthar high-dose group (23/30, 76.7%) compared to the Acthar low-dose group (16/29, 55.2%), P=0.0691. In the Completed Patients Population, the treatment comparison was a Spasm Control Response rates in the Acthar high-dose group (21/26, 80.8 %%) compared to the Acthar low-dose group (4/24, 58.3%), P=0.0782.

- In the mITT and Spasms Populations, the Spasm Control Response rates were higher for patients with cryptogenic IS etiology compared to symptomatic IS etiology in either dose group: Acthar high-dose (7/7, 100% compared to 12/17, 70.6%, respectively) versus Acthar low-dose group (6/9, 66.7% compared to 8/18, 44.4%, respectively).

- An exploratory analysis of relapse suggested that approximately 20% (3/15) of patients in the Acthar high-dose group and 15% (2/13) of patients in the Acthar low-dose group relapsed after treatment.

Questcor Conclusions for CSR 222017-05 efficacy: In the primary, mITT Population, the analysis of the Spasm Control Response by IS etiology showed a statistically significant difference between the Acthar high-dose and Acthar low-dose treatment groups in favor of Acthar high-dose (P=0.0329). This statistical difference in favor of the

Acthar high-dose by IS etiology was also demonstrated in the Spasms Population (P=0.0126).

A trend in favor of the Acthar high-dose group was also demonstrated in the ITT sensitivity analysis (P=0.0691) and in the Completed Patients Population (P=0.0782). In all cases, the Spasm Control Response rates appeared higher in patients with cryptogenic etiology compared to those with a symptomatic etiology in each dose group; however, the study was not designed nor was the study powered to make statistical conclusions about these observed differences based on IS etiology.

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. In addition, the analysis of the secondary endpoint of the remission of the Hypsarrhythmic EEG Pattern Response did not show any statistically significance differences between the 2 treatment groups in any of the defined study populations. As previously stated, this study was underpowered in its ability to demonstrate differences between the 2 treatment groups.

In addition, both the Overall Response endpoint and the Hypsarrhythmic EEG Pattern Response were dependent on the EEG results. As per the study protocol, the 2 dosing groups had different schedules as to when the post-Acthar EEGs were to be performed. The patients randomly assigned to the Acthar low-dose group were scheduled to have their first post-Acthar EEG performed 2 weeks after the start of treatment, whereas patients in the Acthar high-dose group did not have their first post-Acthar EEG performed until after the Acthar was tapered to zero, a full 12 weeks after the initiation of therapy and 9 weeks after the maintenance dose of 150 U/m2/QD had been administered. In addition, there were patients in this study without any evidence of EEG testing after the initiation of Acthar treatment. Of note is that, in this study, Acthar was administered as a once-daily dose of 150 U/m2. 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 (i.e., 75 U/m2 per dose). This difference in the dosing regimens results in a single ACTH plasma peak concentration in CSR 222017-05 compared to 2 ACTH plasma peak concentrations from the twice-daily dosing in CSR 222017-01.
The Sponsor concludes that the data from CSR 222017-05 at least support the efficacy of Acthar high-dose monotherapy with respect to one of the secondary endpoints (the Spasm Control Response)
even when the daily dose was administered once a day rather than as a divided dose administered twice a day as in CSR 222017-01.

Reviewer Note:
As discussed previously in this review, the endpoint of clinical interest is the combined endpoint (Overall Response) of both spasm cessation and

disappearance of hypsarrhythmia (the endpoint used in the pivotal study). There is no statistical significant difference between the two arms for this combined endpoint.

Why was there a lower response rate for the high dose arm in this supportive study compared to the pivotal study? There may have been differences in the patient population although the inclusion/exclusion criteria are similar. The most likely explanation seems to be that the pivotal study used a BID dosage for the high dose Acthar Gel which would be expected to give a more sustained ACTH levels and a greater cortisol response

Assuming that the BID dosage accounts for the higher response rate for the high dose (150 U/m2/day) seen in the pivotal study (CSR 222017-01) in comparison to the supportive study (CSR 222017-05) and also assuming that the CSR 222017-05 secondary endpoint of spasm control response indicates greater efficacy from the high dose arm compared to that of the low dose arm, the use of the high dose dosage given BID (as in the pivotal study can be considered to be supported over the use of a lower dose or a QD dose. However, the data is not as definitive as it would have been in a prospective contemporaneous dose response study of several doses in a single randomized population of infants with IS.

Additional Data Analysis to Assess Acthar Efficacy: CSR 222017-04 (Hrachovy, 1983)

Questcor was also able to obtain the primary study data from a second clinical trial by Dr. Hrachovy and colleagues entitled, “Double-blind Study of ACTH versus Prednisone Therapy in Infantile Spasms.” This study was 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 (CSR 222017-04).

Eligibility Criteria: Patients enrolled in the study were diagnosed with IS (clinical spasms with hypsarrhythmic EEG patterns). All study patients were under the age of 4 years, had onset of spasms prior to age 12 months, and had spasms ongoing at the time of entry into the study. An infant previously treated with any steroid or ACTH or Acthar treatment was not eligible for the study. Informed consent was obtained from each patient’s parent or guardian.

Evaluations: Before the initiation of treatment, patients were monitored for 24 to 48 hours to confirm the presence of IS and to establish a baseline seizure frequency. Patients were monitored at 2 weeks and at 6 weeks after discontinuation of therapy. Patients were evaluated throughout the study for safety.

Treatment Protocol: Patients were randomly assigned to receive Acthar 20 U/QD IM and a prednisone placebo PO or prednisone 2 mg/kg/day PO and an Acthar placebo IM, for 2 weeks. Acthar 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 either changed to the other study drug (Acthar 30 U/QD or prednisone 2 mg/kg/day) or the originally assigned treatment was continued; this treatment was continued 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 to the additional 4 weeks of therapy as were then crossed over to the other drug after a 1-week washout period and the protocol was repeated. Efficacy Measures: 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 EEG monitoring.

Reviewers of the serial long-term EEG and video monitoring studies were unaware of patients' treatment group assignment. Secondary endpoints included in the analysis included EEG changes in nonresponders and changes in mental and developmental status.

Results: Twenty-four patients were enrolled in the study; 12 patients were randomly assigned to Acthar low-dose and prednisone placebo, and 12 patients were randomly assigned to prednisone and an Acthar placebo. A total of 19 patients (19/24, 79.2%) had symptomatic etiology of IS and 5 patients (5/24, 20.8%) had cryptogenic etiology of IS.

Questcor's analysis of the efficacy data demonstrated that the overall response rates in the initial treatment phase were 5/12 (41.7%) for Acthar low-dose and 4/12 (33.3%) for prednisone. The 95% 2-sided confidence intervals for the initial phase overall response were (15.2%, 72.3%) and (9.9%, 65.1%), respectively. Overall response rates were greater than the historical comparator rate of 5% for spontaneous remission through 3 months and 11% through 6 months (Hrachovy 1991) and were better than the placebo rate of 5% reported in a placebo-controlled, randomized, controlled trial of vigabatrin comparing the response rate (complete elimination of spasms and hypsarrhythmia) (Appleton 1999).

The overall response rates reported in this study, suggest that both therapies have some efficacy in the treatment of this disorder.

Conclusions: The overall response seen in these analyses to both Acthar low-dose and prednisone was similar between the 2 treatments. The response rates were higher than the reported spontaneous remission rates for this disease. These data indicated that both therapies provide some degree of efficacy for the treatment of patients with IS.

Reviewer Note:

There was no statistical difference between the two arms of the study. Although the comparison to the historical placebo spontaneous remission rate and to the placebo arm of the Appleton vigabatrin study (which had a different primary outcome) is interesting and somewhat reassuring, it is not conclusive. Therefore, the Sponsor is correct in considering this study as "additional data" rather than a pivotal or supportive study.

Safety Studies

See section 7.1.1 of this review for a discussion of the studies used for safety analysis.

6 Review of Efficacy

6.1 Indication

Infantile Spasms

6.1.1 Methods

Because only one study was presented as pivotal, only one study as supportive, and only one study as additional evidence of efficacy, the three studies' results are presented individually. Each study is discussed in detail in section 5.3 of this review.

6.1.2 Demographics

See section 5.3 for each study

6.1.3 Subject Disposition

See section 5.3 for each study

6.1.4 Analysis of Primary Endpoint(s)

Table 1 Comparison of Response Rates across All Three Studies

(from the Agency's Statistical Review by Dr. Zhang)

	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

6.1.5 Analysis of Secondary Endpoints(s)

See section 5.3 for each study

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

The small number of patients did not allow for a meaningful comparison of the response of patients with cryptogenic vs. symptomatic infantile spasms.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No dose response study was performed.

The "additional evidence" efficacy study, CSR 222017-04, studied Acthar low-dose 20 U/day (the same daily dose of Acthar Gel studied in CSR 222017-05) compared to the prednisone 2 mg/kg/day (the same daily dose of prednisone studied in CSR 222017-

01). The data from CSR 222017-04 revealed no difference in the overall response between the patients randomized to Acthar low-dose compared to the patients randomized to prednisone. Of interest in this CSR 222017-04 study is that the response rate for the Acthar low-dose group of 5/12 (41.7%) was approximately the same response rate as was reported for the Acthar low-dose patients in the CSR 222017-05 mITT Population of 13/27 (48.1%). Similarly, the overall response for the prednisone patients in CSR 222017-04 of 4/12 (33.3%) is approximately the same response rate as was reported for the prednisone patients in CSR 222017-01 of 4/14 (28.6%). The concordance of the response rates of the two arms of CSR 222017-04 to the results seen with similar treatment arms in the two other studies, CSR 222017-01 and CSR 222017-05, provides some confirmation of the conclusions reached in the pivotal (CSR 222017-01) and supportive (CSR 222017-05) efficacy studies.

However, the data is not as definitive as it would have been in a prospective contemporaneous dose response study of several doses in a single randomized population of infants with IS.

6.1.9 Discussion of Persistence of Efficacy (Relapse) and/or Tolerance Effects

Given the relatively short-term treatment of 4 weeks (2 weeks of high dose with a two week taper) proposed in this NDA, it is important to consider what the relapse rate is after treatment is stopped. Unfortunately, the relapse data is very limited.

CSR 222017-01 (Baram 1996)

The publication and the clinical study report with protocol from the pivotal study CSR 222017-01 (Baram 1996) do not indicate how relapses were determined. The Sponsor was asked about method of recurrence detection on March 19, 2010 and replied that this could not be determined. For the purpose of my review, it is assumed that detection of a recurrence of spasms was based on caretakers notifying the investigators who may or may not have verified the recurrence with a video-EEG study. The fact that recurrence of spasms would be an “all-or-none” phenomenon suggests that the caretakers would be reasonably likely to detect a recurrence of spasms which would recur in clusters rather than subtle isolated spasms. Table 2 of the Baram publication shows that two of the 13 patients who responded to Acthar gel relapsed (a symptomatic female infant treated at 3 months of age and followed-up for 2 months; a symptomatic male infant treated at 6 months of age and followed-up for 17 months). This suggests a relapse rate of at least 2/13 (15%) but there is no indication as to how many months after treatment the recurrence was observed. Of the remaining 11 infants who responded to Acthar gel, 3 had no reported recurrence but were only followed for 1 month after treatment and 8 had no reported recurrence after being followed for 6 months or more (mean 17 months, range 6-37 months). Thus, it is possible that the

recurrence rate was higher if one assumes that one or more of the infants with short follow-up times had a recurrence occurring after the time of follow-up with the investigators.

CSR 222017-05 (Hrachovy 1994)

The supportive efficacy study CSR 222017-05 (Hrachovy 1994) relied on caregiver report to detect relapse after the treatment period. If the caregiver reported relapse, this was verified with video-EEG monitoring. In the completed patient population, 13/26 high dose patients responded and 14/24 low dose patients responded. The relapse rate for the high dose arm responders was 2/13 patients (15%). In the published article, the relapse rate for the low dose arm responders was 3/14 patients (21%). There was no statistical difference between these relapse rates. Questcor re-analyzed the data using the response data for the mITT population and found similar relapse rates: 3/15 (20%) of responders in the high dose arm relapsed and 2/13 (15%) of the responders in the low dose arm relapsed.

Reviewer Note:

Although very limited, the relapse rate data suggests a relapse rate in the range of 15 to 30%. This is similar to the relapse rate range observed in studies of oral vigabatrin presented at the FDA Advisory Committee of January 2009.

Additional Discussion submitted by the Sponsor on June 8, 2010

In response to the Agency's request following the Advisory Committee meeting (section 9.3 of this review), the Sponsor submitted a paper entitled (b) (4)

The Sponsor addressed issues concerning relapse rates and possible retreatment with Acthar Gel:

The Sponsor concluded that the relapse rate is between 15-21% for patients who have a combined response of cessation of spasm and elimination of hypsarrhythmia on EEG. This is based on the studies summarized in the following table from the June 8 submission.

Study	Type of Study: Treatments	Acthar/Comparator Dose	# of Patients	Response Rate	Relapse Rate	Average±SD (Range) Time of Follow-Up [months]
Baram 96	RCT: Acthar vs.	150 U/m^2 /d (75U/m^2 BID)	15	87%	15%	15.1±13.66 (2-48)
	Prednisone	2mg/kg (1 mg BID)	14	27%	NR	16.9±14.39 (2-46)
Snead 83	Retrospective: Acthar	150 U/m^2 /d (75U/m^2 BID)	30	97%	20%	24.6
	vs. Prednisone	3 mg/kg/d	22	50%	15%	47.1
Snead 89	Prospective: Acthar	150 U/m^2 /d (75U/m^2 BID)	15	93%	14%	43.3
Hrachovy 94*	RCT: Acthar Low Dose	20 U QD (≈50U/m^2 QD)	26	58%	21%	1.9±0.47 (0.5-2.6)
	vs. Acthar High Dose	150 U/m^2 QD	24	50%	15%	3.1±1.55 (1.4-9.5)
Hrachovy 83#	RCT: Acthar vs.	20 U QD (≈50U/m^2 QD)	12	42%	33%	12-33
	Prednisone	2 mg/kg QD	12	33%	28%	12-33
		Acthar Patients	122	89/122 (73%)	18/89 (20%)	

NR = Not reported
* Time to follow-up data was not included in the publication: this data was calculated based on Questcor's analyses (CSR 222107-05)
# The complex design of this study and the data provided did not allow Questcor to calculate a relapse rate or even confirm these published relapse rates

Reviewer Note:

The Baram 96, Hrachovy 94, and Hrachovy 83 studies in the table correspond to Studies 01, 05, and 04 respectively as discussed in this review. The table is essentially the same as slide CE-10 presented as a PowerPoint presentation at the Advisory Committee.

As the Sponsor points out, only Study 05 (Hrachovy 95) has the relapse data in the publication based on the mITT population who had achieved the combined response). The Sponsor comments that Dr. Baram (pivotal study -01) did not have data on relapse in the clinical study report data-base; however, a relapse rate of 15% is given apparently based on the same criteria I used at the beginning of this section o my review which was available in draft to the sponsor just prior to the Advisory Committee. As noted above, the recurrence rate for the Baram study -01 could be higher given that 3 of the infants only had a 1 month follow-up after responding to therapy

The Sponsor notes that the relapse rate for study -04 (Hrachovy 83) is higher (33%). The Sponsor suggests this may be due to the ;lower dose of Acthar Gel used in this study compared to the pivotal Baram study (although the dose is the same as in Hrachovy 94 study -05 and although the prednisone relapse rate is also higher despite being the same as in the Baram study). An alternative explanation may be that all patients in this study had at least 12 months of follow-up whereas some of the patients in studies -01 and -05 only had as little as 1-2 months of follow-up as indicated in the range of follow-up in the last column of the table.

In spite of the shortcomings of the data in the table, it seems reasonable to conclude with the Sponsor that the relapse rate is about 15-33% in patients who had a combined response.

The Sponsor notes that the time to relapse cannot be determined form the study data. However, the sponsor states that their consultants'' experience indicates that relapse occurs typically within 2-3 months after response and that recurrence after 6 months is rare. This also reflects the experience of the pediatric neurologist members of the Advisory "committee expressed during discussion.

The Sponsor concluded that lower relapse rates and improved long-term outcome are related to how quickly a patient achieves Overall Response on Acthar after a diagnosis of Infantile Spasms.

Reviewer Note:

The Sponsor reviews the medical literature that supports the current clinical practice consensus that infants treated within 1 month of appearance of the spasms have a somewhat higher response rate and somewhat improved prognosis. As previously discussed this data is suggestive but not conclusive.

The Sponsor concludes that "(b) (4)".

Reviewer Note:

This seems reasonable, but is not conclusive. As discussed above, this is not based on study data but on the clinical experience of the Sponsor's consultants.

The Sponsor concludes that retreatment with Acthar Gel after a recurrence should be a decision made by the physician and parent. Ther sponsor concludes that the following factors should be taken into account in assessing the risk/benefit o retreatment:

(b) (4)

Reviewer Note:
The Sponsor addresses several clinical scenarios. The Sponsor notes that no trials or cohort studies directly address this issue. Some studies allowed for retreatment and this data is cited as supportive of the conclusion. The conclusion is based largely on their consultants' experience rather than adequate data; although it seems reasonable given our current state of knowledge, it is not conclusive. Therefore, this particular approach to clinical practice should not be included in the labeling to the exclusion of other reasonable approaches.

6.1.10 Additional Efficacy Issues/Analyses
The Sponsor concludes that the evidence presented in this Complete Response from the independent analyses of the data obtained in studies conducted by Drs. Baram (CSR 222017-01) and Hrachovy (CSR 222017-05 and CSR 222017-04), together with the AAN Practice Parameter recommendation (Mackay 2004) and the published literature, all support Acthar as an effective treatment for patients with IS. These data, when considered in their entirety, support the approval of Acthar for the IS indication.

The pivotal efficacy study, CSR 222017-01, demonstrated that Acthar at a dose of 150 U/m2/day administered as 75 U/m2/bid IM for 2 weeks followed by a 2-week taper was superior to prednisone 2 mg/kg/day administered as 1 mg/kg/bid in patients with IS as determined by the overall response of spasm cessation and resolution of the hypsarrhythmia pattern on EEG (13/15, 86.7% versus 4/14, 28.6%, respectively, P=0.0015). This study also showed a statistically significant difference in the spasm cessation response alone (P=0.0015) and in the resolution of the hypsarrhythmia pattern on EEG (P=0003) in favor of the patients randomized to receive Acthar compared to those randomized to receive prednisone. These significant differences, seen in such a small study, provide convincing and clear-cut evidence of the efficacy of Acthar at the studied dose of 150 U/m2/day administered IM in 2 divided doses for 2 weeks followed by a 2-week taper in the treatment of IS patients.

The supportive efficacy study, CSR 222017-05 studied 2 doses of Acthar in patients with IS. The Acthar high-dose regimen consisted of treatment with Acthar as a single daily dose of 150 U/m2/QD for 3 weeks, followed by a 9-week taper. The Acthar low-dose regimen consisted of treatment with Acthar as a single daily dose of 20 U/QD for 2 weeks. Patients in the Acthar high-dose arm were not assessed for efficacy using an EEG assessment until the full 12 weeks of treatment whereas patients in the Acthar low-dose group had an EEG after 2 weeks of treatment with an upward dose adjustment to 30 U/QD for 4 additional weeks if spasms and/or the hypsarrhythmic EEG pattern persisted or the dose was tapered if the patient had responded to the Acthar low-dose treatment based on both spasms cessation and resolution of the hypsarrhythmic EEG pattern. It is likely that the study design difference in the timing of

the post treatment EEG assessment (patients who received Acthar high-dose regimen in this study were not to be re-assessed for EEG response until the full 12 weeks of Acthar therapy, whereas patients in the Acthar low dose arm had their first post treatment EEG assessment 2 weeks after starting treatment) had negatively impacted the ability for the Acthar high-dose patients to meet the primary efficacy endpoint in this study, the Overall Response (cessation of spasms and resolution of the hypsarrhythmic EEG pattern). The fact that this study demonstrated a statistically significant difference in the Spasm Control Response in the mITT Population (the primary study population) as well as the Spasms Population with a trend toward this result in the other 2 supportive populations, the ITT Population (used for the sensitivity analysis) and the Completed Patients Population, demonstrate that the Acthar high-dose treatment was more efficacious than the Acthar low-dose treatment, particularly when taking into account the EEG measurement issues described above.

The additional efficacy study, CSR 222017-04, studied Acthar low-dose 20 U/day (the same daily dose studied in CSR 222017-05) compared to the prednisone 2 mg/kg/day (the same daily dose studied in CSR 222017-01). The data from CSR 222017-04 revealed no difference in the overall response between the patients randomized to Acthar low-dose compared to the patients randomized to prednisone. Of interest in this study is that the response rate for the Acthar low-dose group of 5/12 (41.7%) was approximately the same response rate as was reported for the Acthar low-dose patients in the mITT Population CSR 222017-05 of 13/27 (48.1%). Similarly, the overall response for the prednisone patients in CSR 222017-04 of 4/12 (33.3%) is approximately the same response rate as was reported for the prednisone patients in CSR 222017-01 of 4/14 (28.6%). The concordance of the response rates of the two arms of CSR 222017-04 to the results seen with similar treatment arms in the two other studies, CSR 222017-01 and CSR 222017-05, provides some confirmation of the conclusions reached in the pivotal (CSR 222017-01) and supportive (CSR 222017-05) efficacy studies in this NDA.

7 Review of Safety

Safety Summary

Reviewer Note: The Sponsor notified the Agency in a teleconference on March 22 that it intended to revise the "treatment groups" (dose categories based on the maximal daily dose of Acthar Gel received) used to integrate the safety data across safety studies in their NDA submission (see 7.1.3 and 7.2.1 of this review). This means that the safety summary tables concerning the 319 patients (see section 7.1.1 of this review) in the Sponsor's briefing document for the Advisory

Committee differ slightly from the summary tables presented in their NDA submission and reviewed in this review.

7.1 Methods

This section reviews the safety data presented by the Sponsor in the integrated summary of safety, in the clinical study reports from the individual studies cited in section 7.1.1 below, and from the published articles from the three studies discussed in the efficacy section of this review.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Questcor could not obtain safety data from the pivotal study (CSR222-017-01, Baram) although these patients are presumed to be among the patients evaluated in the retrospective chart review by Partikian and Mitchell discussed below as CSR 222017-02.

Questcor obtained source safety data from the following 4 studies:

A study conducted by Partikian and Mitchell (Partikian 2007). Questcor's analyses of these safety data are presented in this Complete Response as CSR 222017-02. This study presumably contained the safety data for the patients treated in the randomized controlled trial conducted by Baram and reported in this submission as CSR 222017-01.

Questcor also conducted its own protocol to obtain safety data from patients treated at 4 clinical sites in the United States. These data are presented in this Complete Response as CSR QSC007-ACT-002.

Questcor obtained source data from the 2 of the RCTs conducted and published by Hrachovy and colleagues (Hrachovy 1994, Hrachovy 1983); Questcor's independent analyses of these data are presented in this Complete Response as CSR 222017-05 and CSR 222017-04, respectively.

These four studies are shown in the table below.

Study	Description	Number of Acthar Gel-treated patients contributed to Integrated Safety Tables
CSR 222017-02	Partikian and Mitchell retrospective chart review	84

CSR QSC007-ACT-002	Questcor retrospective chart review at 4 sites	178
CSR 222017-05	Hrachovy 1994 Study of Acthar Gel High vs Low Dose (charts reviewed retrospectively for safety data)	57
CSR 222017-04	Hrachovy 1983 study of ACTH vs Prednisone (patients on Acthar gel not identifiable in retrospective chart review)	None
Total patients in Integrated Safety Tables		**319**

The division of the 319 patients into three dosage categories (Questcor Recommended Dose, Other High Dose, and Low Dose) is discussed in section 7.2.1 of this review.

These four studies are summarized in the following paragraphs.

CSR 222017-02

Clinical study report CSR 222017-02, entitled, "Retrospective Analysis of Adverse Events Associated with Treatment of Infantile Spasms with Acthar Gel," was a retrospective chart review. The primary objective of this study was to analyze retrospective data provided by Drs. Partikian and Mitchell to assess the safety and tolerability of Acthar administered using a standard treatment schedule consisting of a treatment phase followed by a taper phase. The secondary objective was to report the safety data from patients reported in the pivotal efficacy study that compared Acthar to prednisone in patients with IS (CSR 222017-01); safety data from these patients were likely contained within the data obtained from Drs. Partikian and Mitchell for this analysis based on the dates of treatment. Questcor obtained the safety data from the investigators, and with the investigators' permission, Questcor performed an independent analysis for submission in this sNDA; these analyses are presented in CSR 222017-02.

Study Design: Drs. Partikian and Mitchell reviewed the charts of all patients with IS (International Classification of Diseases code 345.6) admitted to Children's Hospital of Los Angeles (CHLA) between January 1990 and August 2006 (Partikian 2007). In addition, they identified outpatients from Neurology Division records of patients with IS whose treatment was initiated without hospital admission. Data from the chart review were collected on data collection forms developed by the Investigators. Drs. Partikian

and Mitchell provided these completed forms to Questcor; Questcor then performed its own independent analysis of these data.

Patients were included in the study based on the diagnosis of IS, with spasms confirmed by either clinical observation or on video-EEG, with EEG evidence of classical or modified hypsarrhythmia or multifocal independent spike discharges. Patients with an atypical EEG pattern were included if an attending pediatric neurologist intended to treat the child as having IS based on clinical criteria of spasms with psychomotor regression.

Demographic characteristics and baseline variables included sex, age at onset of spasms and onset of treatment, lag time from onset of spasms to initiation of treatment, etiology, IS history, developmental status, previous treatment with antiepileptic drugs (AEDs), and pre-existing medical conditions. Treatment variables included initial treatment type, drug dosage, and schedule of administration.

Treatment Protocol: Not all patients received Acthar Gel. Treatment choice was made by the attending child neurologist for the individual patient and not by randomization. When Acthar Gel treatment was chosen, Acthar treatment was administered by IM injection according to a standard protocol. The treatment schedule started with 150 U/m2/day divided into 2 daily doses for the first 1 to 2 weeks, and then tapered beginning with 75 U/m2/day for 1 week, then tapered rapidly to an alternate-day schedule for the next 3 to 4 weeks, which was followed by taper-off treatment. Treatment intervals could not be confirmed from the data provided.

Safety Measures: Assessments of safety and tolerability were collected from patient charts at baseline and at 3 follow-up intervals. The first follow-up interval included all visits that occurred 1 to 3 weeks after initiation of treatment. The second follow-up interval included all visits that occurred 4 to 8 weeks after the start of therapy. The third follow-up interval included visits that occurred 3 or more months after treatment initiation. Safety measures included AEs (parent-reported, major, and serious AEs [SAEs], changes in weight and blood pressure [BP]), changes in medication, and development of new seizure during the treatment period.

Results: The Questcor database had data from 130 patients (each receiving either Acthar Gel or an alternative therapy) from the original published study (Partikian 2007), consisting of patients treated at CHLA between January 1990 and August 2006 for IS, and also data from 29 additional patients, consisting of patients with IS treated at CHLA since the end of the original study through April 2008. The 130 patients from the original published study included **20** patients who received Acthar as initial treatment for IS in the era of the Baram 1996 study (Era 1) and **45** patients who received Acthar as initial treatment for IS after the era of the Baram 1996 study (Era 2). Of the 29 additional patients, **19** received Acthar as initial treatment for IS (Era 3).

Therefore, a total of 84 patients (20 + 45 + 19) received Acthar as initial treatment for IS (Overall: Eras 1, 2, and 3, combined). The analysis of safety for patients who received Acthar as initial treatment for IS in this retrospective data review is as follows:

• Parent-reported AEs consisted largely of irritability, excessive appetite, infections, and sleep difficulties. These tended to be reported during the first follow-up interval, when the patients were on the highest dose of drug, and decreased over time as the drug was tapered and discontinued.

• More than 33% (28/84) had at least 1 potentially significant systolic BP (SBP) measurement during the first follow-up interval compared with only 17.9% (15/84) at baseline. The number of patients with potentially significant SBP measurements decreased to 21.4 % and 3.6% during the second (18/84) and third (3/84) follow-up intervals, respectively. The results for diastolic BP (DBP) were similar, where 23.8% (20/84) had potentially significant measurements during the first follow-up interval compared with 14.3% (12/84) of patients at baseline. The number of patients noted to have potentially significant DBP measurements decreased to 10.7% and 4.8% during the second (9/84) and third (4/84) follow-up intervals, respectively.

• The most common SAEs included nervous system disorders, infections, and hospitalizations. The nervous system disorders were all seizure-related, but it was not possible to separate new seizures from exacerbations of the IS or progression of IS to other seizure disorders.

• Common laboratory abnormalities reported included white blood cell elevation, low serum potassium, elevated liver function tests, and low hemoglobin.

Mean change from baseline for weight averaged 11.6%, 17.8%, and 25.7% over the first, second, and third follow-up intervals, respectively. The increases in weight over time may have been due to both background growth in infants as well as to Acthar-induced weight gain.

• Safety results for patients who received Acthar during Era 1, representing patients previously evaluated for efficacy by Questcor (CSR 222017-01), were consistent with the safety findings for the patients who received Acthar in Era 2 and Era 3.

• There were no SAEs reported for patients who received prednisone in Era 1 of this study. This may be related to the fact that these patients appeared to have a shorter duration of therapy when compared to Acthar, possibly due to lack of efficacy of the prednisone treatment for IS.

Sponsor's Conclusions: The AEs reported in this study in patients treated with Acthar are well known to occur with this therapy. None of the findings from this retrospective chart review were unexpected. The AEs reported are readily recognized and managed by routine clinical care and medical interventions. In particular, blood pressure elevations that may occur with Acthar may be managed, if medically necessary, with antihypertensive drug therapy.

CSR QSC007-ACT-002

Clinical study report CSR QSC007-ACT-002, entitled, “Determination of the Adverse Effect Profile for Patients with Infantile Spasms Treated with H.P. Acthar Gel (ACTH): A Retrospective Review,” was a retrospective chart review study to determine the AE profile of patients with IS treated with Acthar. Patients were included in the study based on the diagnosis of IS and age at first treatment with Acthar.

The primary objective of this study was to assess the AE profile in patients with IS treated with Acthar high-dose (approximately 150 U/m2/day [range from 125 to 175 U/m2/day]) given in 2 divided doses administered to patients from January 2000 to 01 May 2008 at 4 participating clinical centers.

Study Design: Data review and capture was planned for the period January 2000 to 01 May 2008. Potential cases were identified by querying the hospital, pharmacy, and/or clinical records for patients from the years 2000 through 2008. The data were extracted from clinic and/or hospital charts including the treating doctors’ notes, EEG reports, magnetic resonance imaging reports, and other clinical information.

For the data analysis, patients were categorized into 1 of 3 treatment groups based on the maximum daily dose of Acthar administered as shown below:
• Questcor Recommended Dose: 150 U/m2/day (Dose range within the range ≥ 135 and ≤ 160 U/m2/day), divided, bid
• Other High Dose: Dose ≥ 80 U/m2/day but outside the Recommended Dose (included patients with a maximum dose ≥ 80 U/m2/day but outside the Recommended Dose range and patients with a maximum dose within the Recommended Dose range that was not administered divided bid)
• Low Dose: Dose < 80 U/m2/day

Treatment Protocol: Acthar treatment was administered by IM injection according to clinical practice at each study site.

Data Methods: Procedures used to collect, to analyze, and to ensure the integrity of study data are provided in the final study report (see CSR QSC007-ACT-002).

Safety Measures: For assessment of AEs, data were collected from patient charts at baseline, at subsequent visits for evaluation of Acthar treatment, and at a final visit. The final visit was defined as any clinic visit that occurred at least 2 weeks following the final dose of Acthar or the last recorded visit at or near 2 weeks.

Results: One hundred and seventy-eight (178) patients were included in the analysis data set. Analysis of data from this retrospective study of patients who received Acthar as treatment for IS demonstrated the following:

- Over half of all patients (59.0%, 105/178) experienced 1 or more AEs during the study. The proportions of patients with 1 or more AE were similar in the Other High Dose and Recommended Dose groups (67/105, 63.8% and 31/50, 62.0%, respectively). The Low Dose group had the smallest proportion of patients with 1 or more AEs (7/23, 30.4%).
- The most common AEs in all groups combined were: irritability (16.3%), Cushingoid appearance (9.6%), hypertension (9.6%), and increased appetite (6.2%). The most common AEs (occurring in >5% of all patients) in the Recommended Dose group were hypertension (18.0%), irritability (12.0%), and left ventricular hypertrophy (LVH) (8.0%). In the Other High Dose group, the most common AEs were irritability (19.0%), Cushingoid appearance (13.3%), increased appetite (10.5%) and hypertension (6.7%). The most common AEs in the Low Dose group were irritability (13.0%), Cushingoid appearance (4.3%), and hypertension (4.3%).
- There were 20 patients overall who experienced 1 or more SAEs during the study, most of which were judged to be related (possibly, likely) and were consistent with the known pharmacology of Acthar. Most patients required no treatment or were adequately treated with medication for the resolution of their SAE.
- One death, due to aspiration pneumonia, was reported in the Other High Dose group and considered to be possibly due to Acthar treatment.
- The most common parent-reported AEs in all patients were irritability, upper gastrointestinal irritability or gastroesophageal reflux disease, infections, drowsiness, sleep difficulties, reduced appetite, respiratory difficulties, excessive appetite, fever, and increased secretions/drooling.
- During the first follow-up interval, 14.0% (25/178) of patients had a planned downward titration of Acthar and 3.9% (7/178) of patients had Acthar decreased prematurely due to an AE. In the second follow-up interval, 73.6% (131/178) of patients had a planned downward titration of Acthar and 0.6% (1/178) of patients had Acthar decreased prematurely due to an AE.
- There were multiple patients with abnormal laboratory values throughout the study; very few resulted in an action being taken by the investigator.
- There were reversible increases in SBP, DBP, and potentially significant BPs during Acthar treatment, which returned to baseline following discontinuation of treatment. These tended to be more frequent in the Recommended Dose group and Other High Dose group compared to the Low Dose group, but the differences between treatment groups were not significant.

Sponsor's Conclusions: Analysis of data from this retrospective study of patients who received Acthar as treatment for IS demonstrated the following:

- The AEs reported in this study are well known to occur with Acthar administration in patients with IS. None of the findings from this retrospective chart review were unexpected.
- The AEs reported were readily recognized and managed by routine clinical care and medical interventions. In particular, blood pressure elevations that occurred with Acthar were readily managed, if medically necessary, with antihypertensive drug therapy.

CSR 222017-05

"High-dose, Long-duration versus Low-dose, Short-duration Corticotropin Therapy for Infantile Spasms" was a prospective, controlled, randomized, single-blind study that compared an Acthar high-dose regimen to Acthar low-dose regimen in patients with IS.

The Acthar high-dose regimen consisted of Acthar given at a dose of 150 U/m2/day as a single IM dose for 3 weeks followed by a 9-week taper; the Acthar low-dose regimen consisted of Acthar 20 U/day as a single IM dose for 2 weeks followed by a 2-week taper in responders or a dose escalation to 30 U/day in nonresponders. The principal investigator, Dr. Hrachovy and his colleagues had previously published the study results from their analyses of the data (Hrachovy 1994). Questcor obtained the source data from the investigators, and with the investigators' permission, Questcor performed an independent analysis for submission in this sNDA; these analyses are presented in the clinical study report CSR 222017-05.

Study Design: Patients enrolled in the study were diagnosed with IS defined by both the presence of clinical spasms and a hypsarrhythmic EEG pattern. All study participants were under the age of 4 years, had onset of spasms prior to the age of 12 months, and continued to have spasms at the time of entry into the study. Patients who had previously received ACTH or Acthar or corticosteroid therapy for their spasms were not eligible for the study. Informed consent was obtained from each patient's parent or guardian.

Prior to the initiation of treatment, patients were monitored using a video-EEG for up to 24 hours in order to confirm the presence of IS and to establish a baseline seizure frequency. Patients were monitored with video-EEGs 2 to 3 times during the treatment period; the treatment period was 12 weeks for the high-dose and 6 weeks for low-dose. As per the study protocol, the 2 dosing groups had different schedules as to when the post-Acthar EEGs were to be performed. The patients randomly assigned to the Acthar low-dose group were scheduled to have their first post-Acthar EEG performed 2 weeks after the start of treatment, whereas patients in the Acthar high-dose group did not have their first post-Acthar EEG performed until after the Acthar was tapered to zero, a full 12 weeks after the initiation of therapy and 9 weeks after the maintenance dose of 150

U/m2/qd had been administered. Patients were evaluated throughout the study for spasm cessation and safety.

Treatment Protocol: Eligible patients were first stratified as having either cryptogenic or symptomatic IS and then randomized to receive treatment with either high-dose Acthar (150 U/m2/day administered as a single daily dose IM for 3 weeks, followed by 80 U/m2/day IM for 2 weeks, then 80 U/m2/qod IM for 3 weeks, then 50 U/m2/qod IM for 1 week, and then Acthar was tapered to zero over 3 weeks) or Acthar low-dose (a single daily dose of 20 U/day IM for 2 weeks). Nonresponders to the high-dose Acthar regimen were treated with prednisone 2 mg/kg/day orally (PO) for 4 to 6 weeks, and then followed in a routine clinical manner. Nonresponders to low-dose Acthar had their Acthar increased to 30 U/day for an additional 4 weeks followed by a taper to zero over a 2-week period.

There were 57 patients in the Safety Population (patients who received at least one dose of Acthar Gel).

Data Methods: Procedures used to collect, to analyze, and to ensure the integrity of study data are provided in the final study report (see CSR 222017-05).

Safety Measures: Patients were monitored for safety throughout the study. Adverse events were recorded to the patient charts as were the results of clinical laboratory evaluations (complete blood count [CBC], blood glucose, electrolytes, urinalysis), vital signs (BP, height, weight, pulse and respiratory rates), concomitant medications, physical examination findings, chest x-rays, and other imaging studies (computed tomography [CT], magnetic resonance imaging [MRI]), as required.

Results:

- The majority of patients (51/57, 89.5%) had 1 or more AEs during the study. The rate of AEs in the Acthar high-dose group (26/28, 92.9%) was similar to that in the Acthar low-dose group (25/29, 86.2%).
- The most frequently reported (≥ 10% of patients) AEs in Acthar-treated patients (high-dose and low-dose) were candidiasis (10/28, 35.7% and 11/29, 37.9%), Cushingoid appearance (8/28, 28.6% and 6/29, 20.7%), otitis media (7/28, 25.0% and 6/29, 20.7%), irritability (4/28, 14.3% and 5/29, 17.2%), pyrexia (5/17.9% and 4/29, 13.8%), acne (6/21.4% and 3/29, 10.3%), diarrhea (6/28, 21.4% and 2/29, 6.9%), blood pressure increase (5/28, 17.9% and 2/29, 6.9%), and vomiting (3/28, 10.7% and 3/29, 10.3%).
- The most frequently reported (≥ 10% of patients) parent-reported AEs in Acthar-treated patients (high-dose and low-dose) at any time during the entire follow-up period were drowsiness (5/28, 17.9% and 3/29, 10.3%), irritability (23/28, 82.1% and 20/29, 69.0%), sleep difficulties (13/28, 46.4% and 10/29, 34.5%), excessive appetite (14/28, 50.0% and 7/29, 24.1%), reduced appetite (12/28, 42.9% and

9/29, 31.0%), infections (11/28, 39.3% and 12/29, 41.4%), fever (8/28, 28.6% and 9/29, 31.0%), and respiratory difficulties (7/28, 25.0% and 3/29, 10.3%).

- The most frequently reported (≥ 10% of patients) physical examination findings in Acthar-treated patients (high-dose and low-dose) at any time during the entire follow-up period were facial rash (15/28, 53.6% and 10/29, 34.5%), thrush (oral) (12/28, 42.9% and 10/29, 34.5%), skin (other rashes, hyperpigmentation) (17/28, 60.7% and 7/29, 24.1%), Cushingoid features (12/28, 42.9% and 10/29, 34.5%), muscular abnormality (7/28, 25.0% and 0/29, 0.0%), and dysmorphic feature (5/28, 17.9% and 2/29, 6.9%).
- There was 1 death in the study. Patient 90-004 was a 3.3 month-old male infant with a history of IS, microcephaly, and severe developmental delay at the start of treatment who was repeatedly hospitalized with severe respiratory symptoms, developed pulmonary edema, respiratory failure, and died of cardiac arrest at 4.5 months of age. The patient was treated with Acthar doses of 20 to 40 U/qd over several weeks.
- Nine (9) patients (4 Acthar high-dose, 5 Acthar low-dose) had 1 or more SAEs during the study. Serious AEs in the Acthar high-dose group were dehydration, bronchopneumonia, increased blood pressure, skin discoloration, and decreased appetite. Serious AEs in the Acthar low-dose group were bronchiolitis, acute respiratory distress syndrome, pneumonia, pulmonary edema, respiratory failure, and cardiac arrest, status epilepticus, otitis media, dyspnea, and cellulitis.
- There was no difference between the 2 dose groups in the number of patients who discontinued the study early due to AEs. Four (4) patients (1 Acthar high-dose, 3 Acthar low-dose) had 1 or more AEs leading to discontinuation during the study. The AEs were increased blood pressure and skin discoloration in the patients in the Acthar high dose group, and pyrexia, increased blood pressure, and otitis media in the patients in the Acthar low-dose group.

Sponsor's Conclusions: The AEs in this study reported in patients assigned to the Acthar high-dose regimen are well known and are readily managed by routine clinical care and routine medical intervention. Acthar high-dose has an acceptable benefit-risk profile for the treatment of patients with IS, particularly given the catastrophic nature of this disorder if left untreated.

CSR 222017-04

Questcor was also able to obtain the primary study data from a second clinical trial by Dr. Hrachovy and colleagues entitled, "Double-blind Study of ACTH [Acthar] versus Prednisone Therapy in Infantile Spasms." This study was a randomized, controlled, double-blind study that compared Acthar at a dose of 20 to 30 U/day given IM as a single daily dose (Acthar low-dose) to oral prednisone 2 mg/kg/day in patients with IS.

Reviewer Note: As discussed below under "Results" of this study, the safety data from these CSR 222017-04 patients could not be included in the integrated safety tables since the treatment arm to which each patient had been assigned could not be determined during the retrospective chart review for safety data.

Eligibility Criteria: Patients enrolled in the study were diagnosed with IS (clinical spasms with hypsarrhythmic EEG patterns). All study patients were under the age of 4 years, had onset of spasms prior to age l2 months, and had spasms ongoing at the time of entry into the study. An infant previously treated with any steroid, Acthar or ACTH treatment was not eligible for the study. Informed consent was obtained from each patient's parent or guardian.

Evaluations: Before the initiation of treatment, patients were monitored for 24 to 48 hours to confirm the presence of IS and to establish a baseline seizure frequency. Patients were monitored at 2 weeks and at 6 weeks after discontinuation of therapy. Patients were evaluated throughout the study for safety.

Treatment Protocol: Patients were randomly assigned to receive Acthar low-dose 20 U/day IM and a prednisone placebo PO or prednisone 2 mg/kg/day PO and an Acthar placebo IM, for 2 weeks. Acthar low-dose and matching placebo were administered as a single dose/day. Prednisone (2 mg/kg/day) and matching placebo were administered as a single dose/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 either changed to the other study drug (Acthar 30 U/day or prednisone 2 mg/kg/day) or the originally assigned treatment was continued; this treatment was continued 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 to the additional 4 weeks of therapy as were then crossed over to the other drug after a 1-week washout period and the protocol was repeated.

Safety Measures: Safety was evaluated throughout the study. The Questcor analysis, however, only included the safety measures that were reported in the study publication, specifically, the incidence of sustained high BP > 140/90 mmHg and cerebral shrinkage. **When the patient charts were obtained for a retrospective chart review for safety data (as had been done with CSR 222017-05), there was no method to determine into which treatment arm the patients had been assigned.**

Results: Twenty-four patients were enrolled in the study; 12 patients were randomly assigned to Acthar low-dose and prednisone placebo, and 12 patients were randomly assigned to prednisone and an Acthar placebo. A total of 19 patients (19/24, 79.2%) had symptomatic etiology of IS and 5 patients (5/24, 20.8%) had cryptogenic etiology of IS.

With respect to safety, limitations of the data available from the chart review did not permit confirmation of published results. Specifically, the data on adverse findings were not attributable to one arm of the study versus the other (low dose ACTH vs oral prednisone). Therefore, this data from CSR 222017-04 was not integrated into the integrated safety results of the three other studies [CSR 222017-02, the Questcor Retrospective Safety Study (CSR QSC007-ACT-002), and CSR 222017-05].

Questcor's analysis of the safety data demonstrated the following:
- Isolated instances of elevated BP >140/90 mmHg occurred during the study but no information was available to confirm that there were sustained elevations in BP.
- The numbers of patients with CT scans showing evidence of brain shrinkage were too few in number to draw any conclusions regarding the effect of treatment.

Sponsor's Conclusions: With respect to safety, limitations of the data available from the chart review did not permit confirmation of published results.

- Patients treated with Acthar or prednisone showed evidence of increased ventricular size or increased subarachnoid space, or both. The numbers of patients with CT scans showing evidence of brain shrinkage were too few in number to draw any conclusions regarding the effect of treatment.
- Hypertension developed with both Acthar and prednisone treatment. Isolated instances of elevated BP >140/90 mmHg occurred during the study but no information was available to confirm that there were sustained elevations in BP.

Reviewer's comment:

NDA submissions usually have blinded prospective safety data from pivotal trials collected during the study according to a prospective protocol. This quality of safety data is not available for this submission.

Supportive study CSR 222017-05 was a prospective efficacy study but the safety data was collected by an unblinded retrospective chart review of the participating patients according to a retrospective protocol for collection for safety data. A similar retrospective chart review was not possible for pivotal study CSR 222017-01 or for study CSR 222017-04 as discussed above.

Studies CSR 222017-02 and CSR QSC007-ACT-002 are retrospective chart reviews of larger numbers of patients the majority of which were not enrolled in a clinical study. They offer a larger, arguably more representative sample of the proposed treatment population.

7.1.2 Categorization of Adverse Events

Serious adverse events were those adverse evetns that required that the patient have an emergency room visit and/or hospitalization.
Significant adverse events were those occurring in ≥ 2% of the total patients (319 patients).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The study population in the analysis of safety integrated across clinical studies included patients from 3 of the 4 clinical studies from which safety data were available [CSR 222017-02, the Questcor Retrospective Safety Study (CSR QSC007-ACT-002), and CSR 222017-05].

Safety data from CSR 222017-04 were not included in the integrated safety summary because of the inability to clearly identify and link the AEs to the specific study treatments evaluated in this particular trial, i.e., Acthar low-dose or prednisone; consequently, these data are presented separately at the end of section 7.1.1 of this review.

Integration of safety data from the above-mentioned 3 studies was performed based on the maximum daily dose of Acthar received by patients at the start of treatment. Patients were categorized into treatment groups based on the maximum daily dose of Acthar received regardless of any prior treatment received before Acthar initiation. Dose categories corresponded with Acthar dose in the proposed label for the treatment of IS (Questcor Recommended Dose) as well as with other dose categories commonly reported in the literature (Other High Dose and Low Dose) as follows:

- Questcor Recommended Dose: Acthar dose of 150 U/m2/day (dose range within the range ≥ 135 to ≤ 160 U/m2/day), divided, bid, administered for 2 weeks
- Other High Dose: Acthar dose ≥ 80 U/m2/day (included patients with a maximum dose ≥ 80 U/m2/day and patients within the Questcor Recommended Dose range where Acthar was not administered as a divided, twice-daily dose)
- Low Dose: Acthar dose <80 U/m2/day (this includes patients who received Acthar 20 U/day in CSR 222017-05)

The designation of the dosing categories, “Other High Dose” and “Low Dose,” was established by Questcor to define Acthar dosing schedules that were different from the Questcor proposed dosing schedule. These designations, “Other High Dose” and “Low Dose,” were based on an arbitrary daily dose of 80 U/m2/day. In addition, patients included in the “Other High Dose” category received a daily Acthar dose that may have been 150 U/m2/day, but the drug was administered as a single daily dose instead of as 2 divided doses, the Questcor recommended dosing schedule.

In all cases where the dose administered to the patient was presented as U/day, Questcor did calculations to present the dose as U/m2/day. These calculations were based upon the data provided in the patient charts. Questcor calculations revealed that patients who received the Questcor proposed dosing schedule of 150 U/m2/day revealed an actual dose range of 135 to 160 U/m2/day (likely due to practical issues around the withdrawal of the actual Acthar dose from the drug vial). Therefore, for this integrated safety summary, the Recommended Dose group of 150 U/m2/day dosing schedule included patients whose actual dose ranged from 135 to 160 U/m2/day administered IM in 2 divided doses.
All safety data presented in this section reflect data integrated from 3 of the 4 studies.

7.2 Adequacy of Safety Assessments

See discussion in section 3.1 of this review concerning safety data quality.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The number of patients from each study that contributed data to each treatment group is shown in Sponsor’s Table

1.1.

Table 1.1 Numbers of Patients from Clinical Safety Studies Contributing Data to Integrated Analysis

Study	Questcor Recommended Dose[a] n=134	Other High Dose[a] n=133	Low Dose[a] n=52	All Patients[a] N=319
CSR 222017-02	84	0	0	84
CSR QSC007-ACT-002	50	105	23	178
CSR 222017-05	0	28	29	57

a. Dose groups are defined in Section 1.4.5.

NOTE: Safety data from the Hrachovy Acthar versus prednisone study (CSR 222017-04) were not included in the integrated summary because of the inability to identify and link the AEs resulting from Acthar or prednisone therapies for the majority of patients.

Source: CSR 222017-02, CSR QSC007-ACT-002, CSR 222017 05

Demographics

Demographics and other baseline characteristics are summarized by treatment group in the sponsor's Table 1.2.
The mean (± standard deviation [SD]) age of all 319 patients at IS diagnosis was 7.7 months (± 5.04 months) and was similar across the 3 treatment groups. Consistent with the known epidemiology of IS, there was a slight preponderance of male patients (187/319, 58.6%).
The mean (± SD) weight of patients was 8.2 kg (± 1.92 kg) and mean (± SD) height of patients was 68.9 cm (± 7.78 cm). The mean (± SD) body surface area (BSA) was 0.397 m2 (± 0.0665 m2). In most patients, information concerning race was not available for analysis (135/319, 42.3%). In those patients with data, the majority were Caucasian (White) (122/319, 38.2%), or African-American (Black) (49/319, 15.4%).

As has been the case in all reported studies, the majority of patients had a symptomatic etiology of IS (189/319, 59.2%). There were, however, a substantial number of cryptogenic cases (122/319, 38.2%) in the study population, which allowed assessment of safety in this group as well.

Table 1.2 Overall Summary of Demographic and Baseline Characteristics by Treatment

Characteristic	Questcor Recommended Dose[a] (n=134)	Other High Dose[a] (n=133)	Low Dose[a] (n=52)	All Patients[a] (N=319)
Age at start of IS treatment (m)				
N[b]	133	126	46	305
Mean	8.2	8.5	9.0	8.4
SD	5.09	5.33	5.78	5.29
Median	7.0	7.5	7.1	7.2
Min, Max	0, 33	1, 36	2, 28	0, 36
Gender, n (%)				
Male	77 (57.5)	74 (55.6)	36 (69.2)	187 (58.6)
Female	57 (42.5)	59 (44.4)	15 (28.8)	131 (41.1)
Race, n (%)				
White	29 (21.6)	70 (52.6)	23 (44.2)	122 (38.2)
Black or African-American	13 (9.7)	27 (20.3)	9 (17.3)	49 (15.4)
Asian	2 (1.5)	4 (3.0)	1 (1.9)	7 (2.2)
Other	2 (1.5)	3 (2.3)	1 (1.9)	6 (1.9)
Unknown	88 (65.7)	29 (21.8)	18 (34.6)	135 (42.3)
Ethnicity, n (%)				
Hispanic or Latino	25 (18.7)	23 (17.3)	11 (21.2)	59 (18.5)
Non-Hispanic or Non-Latino	21 (15.7)	83 (62.4)	19 (36.5)	123 (38.6)
Unknown	88 (65.7)	27 (20.3)	22 (42.3)	137 (42.9)
Height, cm				
N[b]	130	110	42	282
Mean	69.0	68.4	69.8	68.9
SD	7.56	7.63	8.87	7.78
Median	68.3	68.7	69.8	68.7
Min, Max	52, 91	49, 97	55, 90	49, 97
Weight, kg				
N[b]	133	133	51	317
Mean	8.3	8.0	8.5	8.2
SD	1.85	1.83	2.29	1.92
Median	8.4	7.9	8.3	8.2
Min, Max	4, 13	5, 14	4, 14	4, 14

Characteristic	Questcor Recommended Dose[a] (n=134)	Other High Dose[a] (n=133)	Low Dose[a] (n=52)	All Patients[a] (N=319)
Body Surface Area, m^2				
N[b]	134	133	51	318
Mean	0.398	0.392	0.409	0.397
SD	0.0633	0.0640	0.0798	0.0665
Median	0.397	0.389	0.409	0.397
Min, Max	0.24, 0.57	0.25, 0.61	0.26, 0,60	0.24, 0.61
Etiology Category, n (%)				
Cryptogenic	44 (32.8)	57 (42.9)	21 (40.4)	122 (38.2)
Symptomatic	89 (66.4)	71 (53.4)	29 (55.8)	189 (59.2)
Unknown	1 (0.7)	5 (3.8)	2 (3.8)	8 (2.5)

a. Dose groups are defined in Section 1.4.5
b. The number of patients with data available are provided where data were missing for some patients.
Source: Section 1.12.3, Table 6.12.1: CSR 222017-02, CSR QSC007-ACT-002, CSR 222017 05

7.2.2 Explorations for Dose Response

The absence of a formal dose response study is discussed in section 6.1.8 of this review with respect to efficacy.

The integrated safety tables have been formulated with three dose categories discussed in section 7.2.1 of this review.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

Included vital signs, physical and neurological assessment, clinical laboratory assessment as available from retrospective chart review.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Sponsor summarized selected Adverse effects expected from clinical experience with ACTH and steroid medications in Sponsor's Table 1.5 reproduced below.

Table 1.5 Overall Summary of Selected Adverse Events by Treatment Group

Selected Adverse Event	Questcor Recommended Dose[a] (n=134) n (%)	Other High Dose[a] (n=133) n (%)	Low Dose[a] (n=52) n (%)	All Patients[a] (N=319) N (%)
Patients with at least 1 AE	**36 (26.9)**	**77 (57.9)**	**25 (48.1)**	**138 (43.3)**
Patients with No AEs	**98 (73.1)**	**56 (42.1)**	**27 (51.9)**	**181 (56.7)**
Infections	25 (18.7)	32 (24.1)	16 (30.8)	73 (22.9)
Irritability	8 (6.0)	26 (19.5)	8 (15.4)	42 (13.2)
Cushingoid	3 (2.2)	25 (18.8)	8 (15.4)	36 (11.3)
Hypertension	13 (9.7)	16 (12.0)	5 (9.6)	34 (10.7)
Increased appetite	0 (0.0)	12 (9.0)	1 (1.9)	13 (4.1)
Weight gain	1 (0.7)	7 (5.3)	0 (0.0)	8 (2.5)
Cardiac hypertrophy	4 (3.0)	1 (0.8)	0 (0.0)	5 (1.6)
Hyperglycemia	1 (0.7)	2 (1.5)	0 (0.0)	3 (0.9)
Hypokalemia	0 (0.0)	2 (1.5)	0 (0.0)	2 (0.6)

a. Dose groups are defined in Section 1.4.5.
Source: Section 1.12.3, Table 6.12.5,: CSR 222017-02, CSR QSC007-ACT-002, CSR 222017 05

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in the publication (Baram, 1996) of the pivotal efficacy study (CSR 222017-01). Safety data on the patients from this study are presumed to be included in the retrospective safety study by Partikian (CSR 222017-02) which reported only one death. This infant had not been part of the data analysis since the infant did not meet the criteria of being treated for infantile spasms at the author's institution but was subsequently admitted to this institution while being treated with a prolonged 4 month course of Acthar Gel combined with 6 weeks of valproate therapy. This child died of pneumonia attributable to prolonged ACTH therapy.

One death was reported from CSR 222017-05. This infant had a history of microcephaly and severe developmental delay and was randomized at age 3.3 months to the low dose arm of Acthar Gel (20-40 U QD). After repeated hospitalizations with severe respiratory symptoms, the infant died at 4.5 months of age form respiratory failure and cardiac arrest.

One death was reported in the retrospective chart review (QSC007-ACT-002) from aspiration pneumonia possibly related to the "Other High Dose" dose category of Acthar Gel.

Postmarketing surveillance revealed eight other deaths. See 8.3 below.

7.3.2 Nonfatal Serious Adverse Events

Serous adverse events (SAEs) are defined as those requiring an emergency room visit and/or hospitalization. When the chart review of the patient did not indicate the spediifci condition requiring the emergency room visit or hospitalization, the SAE was coded as "emergency care examination" or "hospitalization" in the Sponsor's Table 1.6 reproduced below.

Table 1.6 Overall Summary of Serious Adverse Events by Treatment Group

Serious Adverse Event	Questcor Recommended Dose[a] (n=134) n (%)	Other High Dose[a] (n=133) n (%)	Low Dose[a] (n=52) n (%)	All Patients[a] (N=319) N (%)
Patients with at least 1 SAE	**48 (35.8)**	**10 (7.5)**	**6 (11.5)**	**64 (20.1)**
Patients with No SAEs	**86 (64.2)**	**123 (92.5)**	**46 (88.5)**	**255 (79.9)**
Convulsion	17 (12.7)	1 (0.8)	0 (0.0)	18 (5.6)
Infections	11 (8.2)	2 (1.5)	3 (5.8)	16 (5.0)
Hypertension	10 (7.5)	2 (1.5)	0 (0.0)	12 (3.8)
Hospitalization	6 (4.5)	0 (0.0)	0 (0.0)	6 (1.9)
Pyrexia	3 (2.2)	0 (0.0)	0 (0.0)	3 (0.9)
Diarrhea	1 (0.7)	1 (0.8)	0 (0.0)	2 (0.6)
Vomiting	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.6)
Emergency care examination	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.6)
Decreased appetite	1 (0.7)	1 (0.8)	0 (0.0)	2 (0.6)
Grand mal convulsion	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.6)
Myoclonic epilepsy	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.6)
Dyspnea	1 (0.7)	0 (0.0)	1 (1.9)	2 (0.6)
Pneumonia aspiration	0 (0.0)	2 (1.5)	0 (0.0)	2 (0.6)
Respiratory failure	1 (0.7)	0 (0.0)	1 (1.9)	2 (0.6)
Cardiac arrest	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.3)
Cardiac hypertrophy	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
Diarrhea hemorrhagic	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)

Serious Adverse Event	Questcor Recommended Dose[a] (n=134) n (%)	Other High Dose[a] (n=133) n (%)	Low Dose[a] (n=52) n (%)	All Patients[a] (N=319) N (%)
Gastroesophageal reflux disease	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
Irritability	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Hepatomegaly	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Herpes zoster	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Shunt infection	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Compression fracture	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Biopsy liver	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Acidosis	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Dehydration	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
Osteoporotic fracture	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Complex partial seizures	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Partial seizures	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Status epilepticus	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.3)
Acute respiratory distress syndrome	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.3)
Pulmonary edema	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.3)
Skin discoloration	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
Exposure to communicable disease	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Brain operation	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.3)

a. Dose groups are defined in Section 1.3.

Source: Section 1.12.3, Table 6.12.6, CSR 222017-02, CSR QSC007-ACT-002, CSR 222017 05

7.3.3 Dropouts and/or Discontinuations

The Sponsor provided very limited data concerning drop-outs and discontinuations, presented only in the format of narratives from the four clinical studies discussed in section 7.1.1 of this review.

There was no safety data from pivotal study CSR 22017-01.

The narratives (derived from retrospective chart reviews) from study CSR 22017-02 are often not clear as to whether discontinuations were planned or due to noncompliance or an adverse effect. Most of these patients were not in a clinical study,

The narratives (derived from retrospective chart reviews) from study CSR 22017-05 (Hrachovy 1994) indicated that two of the original 59 patients randomized dropped out before receiving any Acthar Gel (as discussed previously, the safety population was 57). Of the 57 patients, only two narratives indicated discontinuation due to an adverse effect: patient 098-50 (increased blood pressure on high dose).and patient 090-008 (pyrexia on low dose). One patient (090-002) moved to Ohio. One patient (090-007) was lost to follow-up after one dose of low dose. It is not clear why the other three other patients discontinued the study.

The narratives (derived from retrospective chart reviews) from study CSR QSC007-ACT-002 are often not clear as to whether discontinuations were planned or due to noncompliance or an adverse effect. Most of these patients were not in a clinical study,

Patients from study CSR 22017-04 were not included in the integrated summary as previously discussed.7.3.4 Significant Adverse Events

The Sponsor's Table 6.12.4 (reproduced below) shows treatment-emergent adverse effects with an incidence greater than or equal to 2%.

Integrated Summary of Safety for HP Acthar Gel
NDA Supplement for the Treatment of Infantile Spasms

Table 6.12.4 Summary of Treatment-Emergent Adverse Events with Incidence Greater than or Equal to 2%
by MedDRA System Organ Class by Preferred Term by Treatment Group

	Recommended Dose (N=134)	Other High Dose (N=133)	Low Dose (N=52)	All Patients (N=319)
CARDIAC DISORDERS	5 (3.7%)	1 (0.8%)	1 (1.9%)	7 (2.2%)
ENDOCRINE DISORDERS	3 (2.2%)	25 (18.8%)	8 (15.4%)	36 (11.3%)
CUSHINGOID	3 (2.2%)	25 (18.8%)	8 (15.4%)	36 (11.3%)
GASTROINTESTINAL DISORDERS	8 (6.0%)	21 (15.8%)	7 (13.5%)	36 (11.3%)
DIARRHOEA	3 (2.2%)	7 (5.3%)	2 (3.8%)	12 (3.8%)
VOMITING	4 (3.0%)	5 (3.8%)	3 (5.8%)	12 (3.8%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	12 (9.0%)	34 (25.6%)	11 (21.2%)	57 (17.9%)
IRRITABILITY	8 (6.0%)	26 (19.5%)	8 (15.4%)	42 (13.2%)
PYREXIA	6 (4.5%)	8 (6.0%)	4 (7.7%)	18 (5.6%)
INFECTIONS AND INFESTATIONS	27 (20.1%)	32 (24.1%)	17 (32.7%)	76 (23.8%)
INFECTIONS	25 (18.7%)	32 (24.1%)	16 (30.8%)	73 (22.9%)
INVESTIGATIONS	8 (6.0%)	11 (8.3%)	2 (3.8%)	21 (6.6%)
WEIGHT GAIN	1 (0.7%)	7 (5.3%)	0 (0.0%)	8 (2.5%)
METABOLISM AND NUTRITION DISORDERS	9 (6.7%)	22 (16.5%)	4 (7.7%)	35 (11.0%)
INCREASED APPETITE	0 (0.0%)	12 (9.0%)	1 (1.9%)	13 (4.1%)
DECREASED APPETITE	3 (2.2%)	4 (3.0%)	1 (1.9%)	8 (2.5%)
NERVOUS SYSTEM DISORDERS	22 (16.4%)	8 (6.0%)	1 (1.9%)	31 (9.7%)
CONVULSION	17 (12.7%)	4 (3.0%)	0 (0.0%)	21 (6.6%)

Treatment groups defined by maximum dose: Recommended Dose = 150 Divided range from 135 through 160 U/m2/day divided, BID; Other High Dose (>= 80 U/m²/day) excludes the Recommended Dose; and Low Dose (<80 U/m²/day).
All Patients group = (Recommended Dose) + (Other High Dose) + (Low Dose).

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Integrated Summary of Safety for HP Acthar Gel
NDA Supplement for the Treatment of Infantile Spasms

Table 6.12.4 Summary of Treatment-Emergent Adverse Events with Incidence Greater than or Equal to 2% by MedDRA System Organ Class by Preferred Term by Treatment Group

	Recommended Dose (N=134)	Other High Dose (N=133)	Low Dose (N=52)	All Patients (N=319)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5 (3.7%)	14 (10.5%)	7 (13.5%)	26 (8.2%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.7%)	24 (18.0%)	6 (11.5%)	31 (9.7%)
ACNE	0 (0.0%)	10 (7.5%)	3 (5.8%)	13 (4.1%)
RASH	0 (0.0%)	7 (5.3%)	2 (3.8%)	9 (2.8%)
SURGICAL AND MEDICAL PROCEDURES	6 (4.5%)	0 (0.0%)	1 (1.9%)	7 (2.2%)
VASCULAR DISORDERS	13 (9.7%)	17 (12.8%)	5 (9.6%)	35 (11.0%)
HYPERTENSION	13 (9.7%)	16 (12.0%)	5 (9.6%)	34 (10.7%)

Treatment groups defined by maximum dose: Recommended Dose = 150 Divided range from 135 through 160 U/m2/day divided, BID; Other High Dose (>= 80 U/m²/day) excludes the Recommended Dose; and Low Dose (<80 U/m²/day).
All Patients group = (Recommended Dose) + (Other High Dose) + (Low Dose).

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7.3.5 Submission Specific Primary Safety Concerns

See discussion of limitations of the safety data quality in section3.1 of this review.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

See Section 7.3.4 of this review.

7.4.2 Laboratory Findings

The Sponsor did not provide an integrated summary of laboratory findings. These are discussed in section 7.1.1 of this review under the individual safety studies.

7.4.3 Vital Signs

The Sponsor did not provide an integrated summary ofvital signs. These are discussed in section 7.1.1 of this review under the individual safety studies.

7.4.4 Electrocardiograms (ECGs)

ECGs were not routinely done in this infant population.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not evaluated. No adverse reactions attributable to immunogenicity were reported.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See section 7.2.2 of this review

There is a trend for increased adverse effects for higher doses of Acthar Gel especially when given for a treatment period exceeding two weeks with a two week taper. However, dose dependent studies with a prospective collection safety data has not been done.

7.5.2 Time Dependency for Adverse Events

The Partikian (CSR 222017-02) study suggests that some of the steroid-related adverse effects (risk of serious infection, osteopenia) are more likely in treatment courses longer than 2 weeks treatment with 2 weeks for tapering. This is part of the rationale for the proposed dosage. However, the limited data available does not definitively establish the proposed dosage (high dose, short duration) as the optimal one.

7.5.3 Drug-Demographic Interactions

See current labeling.

7.5.4 Drug-Disease Interactions

See current labeling.

The safety data suggest that pre-existing hypertension, congenital infection, other chronic infection or impaired immune status, and some metabolic disorders may be relative contra-indications to the use of Acthar Gel for infantile spasms.

7.5.5 Drug-Drug Interactions

See current labeling.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See current labeling.

7.6.2 Human Reproduction and Pregnancy Data

See current labeling

7.6.3 Pediatrics and Assessment of Effects on Growth

Infantile spasms is a pediatric indication. No assessment of effects on growth has been done.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The sponsor reports there have been no reports of death or symptoms from an acute overdose of Acthar in clinical studies or in the published literature.

There are no systematic studies on the optimal taper period and whether or not there is acute withdrawal and/or rebound from Acthar in the treatment of patients with IS. Like all drugs in the corticosteroid class, it is common practice to taper patients receiving Acthar for the treatment of IS to reduce the possible occurrence of AEs that might be related to abrupt Acthar withdrawal.

The taper regimen suggested by Questcor in the proposed product label is as follows: Taper the dose for 3 days 30 U/m2 in the morning; for 3 days 15 U/m2 in the morning; for 3 days 10 U/m2 in the morning; for 6 days 10 U/m2 every other morning.

8 Postmarket Experience

From 1.5 of ISS

Questcor reviewed and summarized postmarketing surveillance records for Acthar gel including AEs, SAEs, and deaths reported to New Drug Application (NDA) 08-372 from 29 April 1952, when Acthar was approved, through June 2009. This review included all annual reports, periodic AE reports, 15-day alerts, and all follow-up reports submitted to FDA and any other NDA communications and submissions. A summary of the findings related to the safety of Acthar in treating IS reported in postmarketing surveillance records can be found in Section 1.5.2.

Safety data provided in this submission include data from postmarketing surveillance records for Acthar used to treat infants (Questcor Safety Database).

In support of this Complete Response, Questcor thoroughly reviewed in-house safety data for Acthar and AEs reported to NDA 08-372 from 29 April 1952, when the NDA for Acthar was approved, through June 2009. This review included all annual reports, periodic AE reports, 15-day alerts, and follow-up reports submitted to the FDA. Other NDA communications and submissions were also reviewed.

A review of all identified AEs was conducted for patients who had been treated with Acthar or unidentifiable ACTH for the indication of IS, and patients identified as infants by age (28 days through 24 months). In addition to IS, the terms implying the same disorder or a similar condition, such as hypsarrhythmia and myoclonic seizures, were included, in order to obtain the relevant postmarketing information. In these AE reports, the terms originally used to report the AEs were reproduced verbatim or were coded to the preferred term.

8.1 Postmarketing Surveillance Adverse Events Reported for Patients Treated with Acthar

Postmarketing surveillance records (Questcor Safety Database) show a total of 76 patient reports received by the manufacturers and submitted to the FDA for infants treated with Acthar, who experienced 1 or more AE(s).

The most commonly occurring AEs (>2 patients) observed in the postmarketing use of Acthar for the treatment of IS are summarized in the Sponsor's Table 1.8. This table is derived from a tabular summary of all postmarketing AEs provided in Appendix 1.12.5, Table 1.19. A detailed listing of patients and AEs can be found in Appendix 1.12.5, Table 1.18; the list is organized by the date the case was submitted to the NDA.

Table 1.8 Most Common (>2 Patients) AEs Reported to Manufacturer in Infants Treated with Acthar

Body System/Adverse Events (verbatim term)	No. of Patients Reporting AE
Endocrine disorders	
Cushing's syndrome	4
Facial edema	2
Gastrointestinal disorders	
Abdominal distention	2
Vomiting	2
General disorders and administration site conditions	
Drug withdrawal reaction	2
Edema	2
Fever	4
Ineffective therapy	3
Lethargy	2
Infections and infestations	
Oral thrush	2
Sepsis	4
Investigations	
Weight gain	2
Metabolism and nutrition disorders	
Appetite suppression	2
Dehydration	3
Fluid retention	2
Hypokalemia	3
Metabolic alkalosis	3
Nervous system disorders	
Insomnia	2
Seizure	4
Psychiatric (psychic) disorders	
Crying	2
Irritability	5
Respiratory disorders	
Cough	2
Pneumocystis carinii pneumonia	5
Respiratory distress	2

Body System/Adverse Events (verbatim term)	No. of Patients Reporting AE
Skin and subcutaneous tissue disorders	
Acne	2
Rash	6
Vascular disorders	
Hypertension	6

Notes: One patient may have more than one AE. Only one occurrence of an AE was counted for each patient. Adverse events were retrieved verbatim. No recoding was performed.

8.2 Postmarketing Surveillance Serious Adverse Events Reported for Infants Treated with Acthar

Thirty-three of the AE reports received by the manufacturers concerning the use of Acthar in infants were considered serious; these events were submitted to the FDA in 15-day alert reports (serious and unexpected or unlabeled events) or in periodic ADE reports (serious and expected or labeled events). A summary of the SAEs can be found in The Sponsor's Table 1.9.

Table 1.9 Serious Adverse Events Spontaneously Reported for Infants Treated with Acthar

Control No.	Dosing	Serious Adverse Events
M-335	80 U/d	Sepsis[a]
M-339	80 U/d	Sepsis[a]
M-340	80 U/d	Sepsis[a]
M-341	80 U/d	Sepsis[a]
M-342	80 U/d	Hypertension, metabolic alkalosis[a]
M-343	80 U/d	Hypertension, metabolic alkalosis[a]
M-344	80 U/d	Hypertension, metabolic alkalosis[a]
01-001174	150 U/m^2/d –IM Treatment Duration: 3 d Total Dose: 100.8 U	Pyruvate carboxylase deficiency, catastrophic metabolic acidosis, death[b]
01-001652	10 U/kg/d Treatment Duration: 21 d Total Dose: 1764 U	Cushing's ulcer, small fontanel, toxic appearance, abdominal distention, emesis, respiratory distress, fever[b]
01-000941	60 U/d Treatment Duration: 45 d Total Dose: 2700 U	Hypertension, weight gain, motor development delayed
01-008741	50 U/d to 25 U/d Treatment Duration: 30 d Total Dose: 1125 U	Soft/white gums, fever, respiratory failure, seizure, sore throat, death[b]

Control No.	Dosing	Serious Adverse Events
US01-08623/01-011039	56 U/day –IM Treatment duration: 68 d Total dose: 3808 U	Drug withdrawal reaction, appetite suppression, dehydration
US01-08028/01-011040	56 U/day –IM Treatment duration: 81 d Total dose: 4536 U	Drug withdrawal reaction, appetite suppression, dehydration
US01-19053	18 U/day –IM Treatment duration: 7 d Total dose: 126 U	Fever, seizures
US01-19351	20 U/d x 14 d 40 U/d x 14 d 80 U/d x 7 d 40 U/d x 7 d 40 U/qod x 10 d Treatment duration: 52 d Total dose: 1880 U	*P. carinii* pneumonia, septic shock, fluid retention, weight gain, acute tubular necrosis, hypernatremia, hypokalemia, urinary tract infections
US01-19376	70 U/day –IM Treatment duration: 120 d Total dose: 8400 U	*P. carinii* pneumonia, tachypnea, dyspnea, Cushing's syndrome, oral thrush[b]
US01-19380	40 U/day –IM Treatment duration: 90 d Total dose: 3600 U	Cough, respiratory distress, Cushing's syndrome, oral thrush, *P. carinii* pneumonia[b]
US01-19381	80 U/qod – IM Treatment duration: 210 d Total dose: 8400 U	Cough, rhinorrhea, decreased appetite, lethargy, Cushing's syndrome (obesity with acne, hirsutism, purple striae, respiratory distress, hypotonia), *P. carinii* pneumonia, death[b]
US01-19689	80 U/qod x 60 d 80 U/d x 90 d Treatment duration: 150 d Total dose: 9600 U	Mucocutaneous candidiasis, hypertension, bilateral severe pneumonia. (Pneumocystis organisms observed at autopsy), death[b]
US01-20092	20 bid to 30 bid, tapering Treatment duration: 32 d Total dose: 1640 U	Adrenal insufficiency, hypokalemia, cardiac arrest, anoxic brain injury
US01-20137	60 U/d x 21 d 40 U/d x 21 d 20 U/d x 14 d Treatment duration: 21 d to AE + 35 days Total dose: 1260 U to AE + 1120 U	Cardiac hypertrophy, hypertension, right upper lobe pneumonia, pulmonary edema, death[b]
US01-22284	80 U/day – IM Treatment duration: 42 d Total dose: 3360 U	Lethargy, decreased oral intake, rapid respiratory rate, *P. carinii* pneumonia[c]

Control No.	Dosing	Serious Adverse Events
US01-24280	80 U/d x 14 d 120 U/d x 14 d 80 U/d x 14 d 60 U/d x 35 d Treatment duration: 77 d Total dose: 4420 U	Respiratory syncytial virus infection, shortness of breath, fever, interstitial pneumonitis
2000-20713US	40 U bid Treatment duration: 153 d Total dose: 12240 U	Brain shrinkage[c], hydrocephalus
ACT-S0001	30 IU/mL qod – IM Treatment duration: NR	Hypertension, cardiomyopathy
03-ADE-SU-0001-ACT	32 - 16 U/mL qod – IM Treatment duration: NR	Seizure, death
03-ADE-SU-0002-ACT	40 U/d to 20 U/d – IM Treatment duration: NR	Vomiting, respiratory arrest, death[b]
06-ADE-SU-0017-ACT	150 U/m^2/d IM x 2 wk, taper x 2 wk Treatment duration: NR	Encephalitis herpes, disease recurrence
06-ADE-SU-0020-ACT	NR	*P jirovecii* pneumonia
07-ADE-SU-0012-ACT	40 U IM qd Treatment duration: NR	Irritability, convulsions
08-ADE-SU-0003-ACT	40 U IM qd for 6 wks with taper Treatment duration: NR	Dehydration, oral intake reduced, fluid retention, acne
09-ADE-SU-0013-ACT	20 - 40 U IM qd Treatment duration: 43 d	Bronchiolitis, acute respiratory distress syndrome
09-ADE-SU-0011-ACT	NR	Leukemia

Notes:
Reference: Table 1.20 - Listing of SAEs Reported to the Manufacturer in Infants treated with Acthar
NR = Not Reported, IM =Intramuscular; d = day, qd = once/day

a. From 15-day alert and MedWatch forms submitted to FDA. By current reporting standards, these did not meet the current criteria for reportable events, because inadequate information was in the original reports sent to the manufacturer.

b. Report derived from a case described in the medical literature; deaths in literature not listed in Table 1.20: 01-001174, 01-008741, and 03-ADE-SU-0002-ACT.

c. The term brain shrinkage was used here, instead of cerebral atrophy.

8.3 Postmarketing Surveillance Deaths

Eight deaths were reported previously to NDA # 08-372 as part of ongoing postmarketing surveillance and are presented in the Sponsor's Table 1.10.

Table 1.10 Postmarketing Surveillance Summaries of Deaths Reported for Infants Treated with Acthar

Report Date	Control No.	Acthar Dose	Key Verbatim Excerpts from SAE Narratives[a]
13-Apr-90	01-001174[b]	150 U/m^2/day –IM Treatment duration: 3 d Total dose: 100.8 U[c]	The patient died at 12 weeks of age after recurrent episodes of profound acidosis. At autopsy, the brain manifested cystic degeneration and demyelination. According to the reporter, the dramatic rise in alanine levels coincident with ACTH therapy suggests that ACTH played a role in precipitating the catastrophic metabolic acidosis. The patient's physician stated that the infant was symptomatic before ACTH therapy and felt that ACTH may have exacerbated the reaction, but did not cause it. The event report included no opinion regarding a possible causal relationship between the events and Acthar treatment.
05-Oct-95	01-008741	50 U/day to 25 U/d Treatment duration: 30 d Total dose: 1125 U[d]	She experienced seizures while being treated with Acthar, the dose was decreased to 25 U daily and, according to the patient's father, the seizures worsened. The treatment duration at this time was 1 month. The patient was hospitalized with fever and a sore throat, administered oxygen through an oxygen tube, but without effect, and subsequently died. The cause of death reported by the pathologist was neurofibromatosis.
23-Jul-98	US01-19381[b]	80 U/qod – IM Treatment duration: 210 d Total dose: 8400 U	Because of rapid deterioration in respiratory status, trimethoprim-sulfamethoxazole 20 mg/kg/d was administered intravenously and mechanical ventilation started. Tissue from an open-lung biopsy showed severe alveolar damage with hyaline membranes, interstitial fibroblastic proliferation, and the presence of *P. carinii*. Cytomegalovirus was subsequently recovered from cultures of the lung specimen. The patient's condition continued to deteriorate, and he died 10 d after admission.
02-Sep-98	US01-19689[b]	80 U/qod x 60 d 80 U/d x 90 d Treatment duration: 150 d Total dose: 9600 U	Seizures ceased within 4 d. Two months later, seizures recurred, and the Acthar dosage was increased to 80 U/d. Seizure frequency declined, but the patient developed mucocutaneous candidiasis that responded poorly to topical therapy, and he became hypertensive. After 3 months, oral prednisone 1 mg/kg/d was substituted for Acthar with the intent of tapering. Clonazepam was used for seizure control. Two d later, the patient's mother thought he was "congested." The next day, the patient was found dead in his crib. The postmortem examination revealed bilateral severe pneumonia.

Report Date	Control No.	Acthar Dose	Key Verbatim Excerpts from SAE Narratives[a]
28-Oct-98	US01-20137[b]	60 U/d x21 d 40 U/d x 21 d 20 U/d x 14 d Treatment duration: 21 d to AE + 35 d, total treatment was 8 weeks. Total dose: 1260 U to AE + 1120 U	The seizures ceased within 24 hours. Three weeks later, examination revealed severe peripheral edema, tachypnea, hypertension (174 mm Hg systolic), hepatomegaly, and intermittent apnea. The Acthar dose was reduced to 40 U/d, and the systolic blood pressure gradually decreased to 110 mm Hg. An ECG conducted 6 weeks after institution of ACTH revealed no change in the degree of septal and left ventricular freewall hypertrophy, or systolic anterior motion of the mitral valve. The dose of Acthar was reduced to 20 U/d with no return of seizure activity. Cardiomegaly and edema persisted. 8 weeks after the start of Acthar, while at home, the infant became lethargic and pale and died during a nap. Postmortem examination revealed bilateral pulmonary edema, right upper lobe pneumonia, centrilobular hepatic congestion, and periventricular leukomalacia. The heart had severe asymmetric left ventricular hypertrophy without dilation of the chambers.
29-May-03	03-ADE-SU-0001-ACT	16 -32 U/mL qod – IM Treatment duration: NR	The medical history included hypertension. The patient was at home and had responded well to Acthar, with cessation of spasms. At the time of the event, the patient was on a tapering regimen of the drug. According to her family the patient had a uniquely new seizure, stopped breathing, and died suddenly. She could not be resuscitated. The treating physician did not think that Acthar was the cause of the event. The patient was severely neurologically impaired.
29-May-03	03-ADE-SU-0002-ACT	40 U alternating with 20 U qod – IM Treatment duration: NR	The patient was at home, and had responded well to a stable regimen of Acthar, with cessation of spasms. The patient became unresponsive after vomiting, had a respiratory arrest, and could not be resuscitated. The physician considered Acthar unrelated to the event. The patient was severely neurologically impaired. Preliminary verbal autopsy indicated impressive right ventricular hypertrophy, and the brain showed evidence of hypoxic ischemic changes before death. The final autopsy report included no information that would indicate relation of the event to treatment. The most likely cause of death was the patient's congenital cardiac and central nervous system abnormalities.

Report Date	Control No.	Acthar Dose	Key Verbatim Excerpts from SAE Narratives[a]
05 May 09[d]	09-ADE-SU-0013-ACT	20 - 40 U IM qd Treatment duration: 43 d	The patient was a 3.3-month-old male infant with a history of IS, microcephaly, and severe developmental delay at the time treatment with Acthar low-dose (20 U/qd) began on 21 February 1990. On 06 March 1990, the dose of Acthar was increased to 30 U/qd per protocol as the patient continued to have spasms. On (b) (6), the patient was admitted to the (b) (4) with bronchiolitis, acute respiratory distress syndrome, and pneumonia: a diagnosis of RSV was made. The patient improved and was discharged on (b) (6); the records of that admission show that the Acthar dose was 30 U/day. On (b) (6), the patient was readmitted with worsening respiratory symptoms; the records of this admission note the Acthar dose was 40 U/day. The patient improved and was discharged on (b) (6). On 03 April 1990, the dose of Acthar was scheduled to be tapered to 20 U/qd per a note in the patient chart at Baylor by the investigator; however, there is no documentation that this lower dose was ever administered. On (b) (6), the patient was again admitted to the (b) (4) with continuing respiratory symptoms. Despite aggressive care and antibiotic therapy, the patient developed pulmonary edema, respiratory failure, and died of cardiac arrest on (b) (6); the patient was 4.5 months of age at the time of death. The dose of Acthar at this last admission was not documented. The investigator did not assess the relationship of these SAEs to Acthar.

a. This column contains information excerpted verbatim from the SAE narratives of the events that had outcomes of death. Causes of death and physicians' comments about the causality relationships between the death and Acthar or ACTH are included when these data were available.

b. Report derived from a case described in medical literature.

c. Duration per regimen not reported. Total dose assumes 2 weeks at initial dose (50 U), 2 weeks at tapered dose (25 U)

d. Report documented in CSR 222017-05 and submitted via MedWatch.

9 Appendices

9.1 Literature Review/References

Baram TZ, Mitchell WG, Tournay A, Snead OC, Hanson RA, Horton EJ. High-dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study. *Pediatrics*. 1996;97:375-379

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Hrachovy RA, Glaze DG, Frost JD, Jr. A retrospective study of spontaneous remission and long-term outcome in patients with infantile spasms. *Epilepsia*. 1991;32(2):212-214.

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Mackay MT, Weiss SK, Adams-Webber T, Ashwal S, Stephens D, Ballaban-Gill K, et al.American Academy of Neurology; Child Neurology Society. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. *Neurology*. 2004 May 25;62(10):1668 1681.

Partikian A, Mitchell WG. Major adverse events associated with treatment of infantile spasms. *J Child Neurol*. 2007 Dec;22(12):1360-1366.

9.2 Labeling Recommendations

The Division of Endocrine and Metabolic Products (DMEP) has primary responsibility for Acthar Gel and the conversion of the currently approved label to PLR format. The indications under the purview of DNP are the currently approved indication for the treatment of exacerbations of multiple sclerosis and the currently proposed indication for the treatment of infantile spasms, to eliminate spasms and hypsarrhythmia electroencephalogram pattern.

DMEP and DNP have worked together to prepare a revised draft using the Sponsor's April 28, 2010 draft labeling as a base document. Numerous changes have been proposed in this revised draft. The number of indications for Acthar Gel has been

greatly reduced to reflect current usage and evidence of effectiveness. Clarification of the dosing for treatment and tapering for infantile spasms has been requested. The Sponsor is asked to rewrite portions of the Adverse Reactions section (6). A reference to the MedGuide the has been added to the Patient Counseling Information (17). The MedGuide only addresses the infantile spasms indication because of the difficulty in recognizing and treating adverse effects in the infant population.

9.3 Advisory Committee Meeting of May 6, 2010

The Peripheral and Central Nervous System Drugs Advisory Committee met on May 6, 2010.

The vote regarding whether the Sponsor had provided substantial evidence of effectiveness from a single and adequate and well-controlled clinical investigation with confirmatory evidence was 22 affirmative and 1 negative. The effectiveness was in the dual endpoint of cessation of spasm and amelioration of the EEG but not prevention of other seizure types, improvement in long-term developmental outcomes, or any other outcomes.

The vote was more divided regarding whether the Sponsor had submitted evidence to support the view that a short course of treatment provides sustained effectiveness (16 affirmative, 7 negative). The discussion indicated that this vote reflected the committee's concern that data was not provided in order for them to determine if the drug product has been shown to provide sustained effectiveness. The committee recommended that the labeling should state which study the recommended regimen is based on. Other alternative dosing and tapering regimens should be considered for future study but should not delay approval.

The committee agreed that sufficient evidence of the safety of Acthar Gel at an effective dosing regimen had been submitted to allow approval. However discussion emphasized that use of ACTH should be closely monitored for toxicity and that ongoing monitoring and post-marketing surveillance are needed particularly with regard to long-term outcomes.

The committee further recommended:

Labeling should clearly state which adverse events should be monitored, such as blood pressure, relapse, adrenal insufficiency, and infection

The REMS may include: physician education prior to prescribing, patient registry, use of specialty pharmacy, and post-marketing studies to include data on second course outcomes with relapse reporting.

Follow-up to the Advisory Committee

A teleconference was held by the Agency with the Sponsor on May 13, 2010 to follow-up on the issues raised at the Advisory Committee. The Sponsor was asked to provide further data and discussion regarding relapse rates, early versus late initiation of treatment, and retreatment (multiple courses for refractory or relapsing patients) with Acthar Gel for infantile spasms.

In response to this teleconference, the Sponsor submitted on June 8, 2010 a paper entitled (b) (4) . This submission is discussed at the end of section 6.1.9 of this review.

In response to the discussion at the Advisory Committee, the Sponsor submitted on August 27, 2010 a four page paper entitled (b) (4) Sponsor concludes that it would not be practical to conduct a comparison study between these two treatments for four reasons. First, the response rates from the pivotal and supporting studies for Acthar Gel range from 42% to 87%, whereas the response rates for Sabril (from the Sabril label) are only in the range of 16% to 25%. This would make it unlikely that physicians and parents would consent to randomization when both treatments were approved for the infantile spasm indication. Second, physicians and parents would want to choose which treatment is most appropriate for the individual infant given the different profiles of adverse effects rather than allow the infant to undergo study randomization. Third, a noninferiority design study would require more patients than could be reasonably recruited; even a superiority design study would require a study population large enough to make recruitment difficult to complete for this relatively rare syndrome, and the superiority design would imply that equipoise does not exist. Fourth, a comparator study in the tuberous sclerosis population alone would be difficult given that the medical community has concluded that vigabatrin is the treatment of choice for infantile spasms secondary to tuberous sclerosis. Furthermore, extrapolation from the tuberous sclerosis population to all other infantile spasms patients would not be appropriate. After discussion within the Division, it was agreed that the Sponsor's overall point that it would be extremely difficult to recruit enough patients for even a superiority study is valid in light of the recruitment challenges of the studies which supported approval of these two treatments.

Given the Advisory Committee's interest in further studies of optimal dosage for Acthar Gel, (b) (4) (b) (4)

(b) (4)

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/s/

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09/28/2010

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