CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-243

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA #: 21-243

Drug Name: AZULFIDINE EN-tabs ®

Dosage Form: Tablet **Strength:** 500 mg / day **Route/Admin:** Oral

Sponsor: Pharmacia & Upjohn Company

Proposed Indication: The treatment of pediatric patients with pauciarticular, polyarticular, and spondylitic courses of juvenile rheumatoid arthritis who have responded inadequately to salicylates or other nonsteroidal anti-inflammatory drugs

Date Submission: 03/30/2000

Documents Reviewed: Volume 1,2, Electronic files, SAS transport files

Medical Reviewer: Kent Johnson, MD

I. Summary of Major Issues Identified by the Reviewer

Sponsor submitted 1 study (CNT 92-ARAO-002) for the evaluation of AZULFIDINE EN-tabs® for the proposed indication.

1) The sponsor did not follow the protocol specified primary efficacy endpoint nor the protocol specified statistical methods.

2) Analysis following the protocol specified endpoint and methods gives a p-value of 0.08, which is bigger than $p<0.01$ from sponsor's post-hoc analysis.

II. Background and Introduction

The sponsor submitted the current NDA for AZULFIDINE EN-tabs® (sulfasalazine delayed released tablets, USP), for the treatment of Juvenile Rheumatoid Arthritis (JRA). The sponsor currently markets AZULFIDINE EN-tabs (sulfasalazine released tablets, USP) approved under NDA 20-465 and AZULFIDINE® Tablets (sulfasalazine tablets, USP) approved under NDA 7-073 for Rheumatiod Arthritis.

The sponsor submitted results of one study, CTN 92-ARAO-002, titled "The Treatment of Juvenile Chronic Arthritis with Sulfasalazine. A Controlled, Double-Blind, Randomised, Multicenter Study of Sulfasalazine versus Placebo".

III. Study CTN 92-ARAO-002

III.1. Protocol Synopsis

Design
A parallel, multicenter, placebo-controlled, randomized, double-blind study. The treatment duration for each patient was 24 weeks. Patients were randomized into 2 treatment groups, sulfasalazine(SSZ) or placebo group. There were visits in weeks: 0, 2, 4, 6, 8, 10, 12, 18, 24.

Objective
The primary objective of this study was to evaluate the efficacy tolerability and safety of sulphasalazine versus placebo in the management of JCA with regard to the success rate over a six month treatment period in both groups.

Primary efficacy endpoints and statistical analysis methods (as specified in the protocol).
The primary efficacy variable was Success as defined by the following criteria:

a. Improvement of joint count (swelling or tenderness) by 2 grades or to 0 in 30% or more of the responsive joints, with no development of activity in inactive joints, OR:
b. Improvement of joint count (swelling or tenderness) by 2 grades or to 0, in 50% or more of responsive joints, with development of activity in 10% or less of the initially inactive joints.

The primary analysis was to follow the intent-to-treat (ITT) principle. For the treatment withdrawals the last available observation on treatment is carried forward to the remaining visits. The response rate was to be analyzed using a Chi-Square test.

III.2. Sponsor's statistical analyses and results

As shown in table 1, the SSZ and placebo treatment groups were balanced in the demographics. Also, as shown in table 2, no significant differences between treatment groups were found in the baseline scores of the Swollen Joint, Ritchie, and Limitations. A total of 69 patients were enrolled and randomized (35 SSZ, 34 placebo group). Of 69 enrolled patients, 68 were qualified for the Intent-to-Treat analysis of efficacy: one patient from the placebo group was excluded from the efficacy analysis because of ineligibility (incorrect diagnosis). A total of 52 patients (75%) completed the 24-week trial.

Table 1. Demographic

	PLACEBO (N=34)	SZZ (N=35)	P-VALUE
Age (years): mean (SD)	9.7 (3.6)	8.4 (4.4)	0.18
Gender (M/F)	11/23	12/23	0.86
Height (cm): mean (SD)	137 (23)	130 (27)	0.20
Weight (kg): mean (SD)	35.6 (15.1)	30.5 (15.7)	0.17

M=male, F=female, SD=standard deviation
P-VALUEs are of Chi-square, Student's t.

Table 2. Baseline ass ..sment of the Swollen Joint, Ritchie, and Limitations Scores

On set type	POLYARTICULAR			PAUCIARTICULAR		
Scores	Placebo (n=15) mean (SD)	SZZ (n=16) mean (SD)	P-value	Placebo (n=18) mean (SD)	SZZ (n=19) mean (SD)	P-value
Swollen	14.1 (9.8)	19.6 (15.0)	0.25	6.3 (5.2)	4.6 (3.2)	0.24
Ritchie	16.8 (16.6)	7.8 (8.9)	0.08	4.2 (4.5)	2.8 (3.2)	0.29
Limitations	18.5 (26.4)	10.9 (9.2)	0.31	4.1 (5.6)	3.4 (3.5)	0.68

M=male, F=female, SD=standard deviation
P-VALUEs are of Chi-square, Student's t.

The primary efficacy variable used in sponsor's analysis was defined as improvement of the severity score of joint swelling by 2 grades or to 0 in 50% or more of the at baseline involved joints, and if applicable development of activity in 10 percent or less of the other joints, with the restriction that the number of deteriorated joints had to be ≤50 percent of the number of improved joints (note that this definition of response is different from the definition specified in the protocol).

According to this different definition, at the final visit, 69% of the SSZ treated patients have responded to treatment and 45% of the placebo treated patients have responded to treatment, with a p-value of 0.06 for the between group difference. In the NDA, the sponsor also performed a post-hoc repeated measure logistic regression analysis, with random patient effects, but with other independent variable unspecified. This analysis gave a p-value of $p<0.01$.

III.3. Reviewer's statistical analyses

The results following the protocol definitions turned out to be not significant. 80% (28/35) of the SSZ patients and 61% (20/33) of the placebo patients achieved success (p=0.082) – Success is defined as specified in the protocol, at week 24 which is visit 9, with LOCF, and a Chi-Square test was used.

To check the proposed model and the consistency of the primary analysis result, reviewer performed statistical analyses for the subgroups and with additional dependent variables. The numbers and rates of the responses are shown in the Table 3, and the analysis results are shown in the Table 4. When the onset type indicator was included as a factor, and the baseline assessment was included as a factor, the statistical results came out to be similar (p=0.078, p=0.084, respectively) to the result of the analysis without those additional variables which is primary. Moreover, homogeneity test of the strata, which is onset type, using Breslow-Day Test did not show the significance (p=0.496). That is, there is no significant interaction between treatment group and onset type.

Table 3. Results of responses – number of responses and percentage

POPULATION	RESPONSE	TOTAL		POLYARTICULAR		PAUCIARTICULAR	
		SSZ	Placebo	SSZ	Placebo	SSZ	Placebo
ITT	Success	28 (80%)	20 (61%)	11 (69%)	8 (53%)	17 (89%)	12 (67%)
	Not Succ	7 (20%)	13 (39%)	5 (31%)	7 (47%)	2 (11%)	6 (33%)
	Total	35	33	16	15	19	18

Table 4. Efficacy analyses results performed by reviewer

POPULATION	ANALYSIS METHOD	DEPENDENT VARIABLE	P-VALUE
ITT	Chi-Square	Trt group	0.082
		Trt group, Onset type	0.078
	Logistic regression	Trt group, Baseline assessment	0.084
ITT, Polyarticular onset type only	Chi-Square	Trt group	0.386
	Logistic regression	Trt group, Baseline assessment	0.418
ITT, Pauciarticular onset type only	Chi-Square	Trt group	0.097
	Logistic regression	Trt group, Baseline assessment	0.067

IV. Conclusions

The sponsor claims significant effectiveness of the drug ($p<0.01$) in the final report. But, the sponsor's analysis did not follow the protocol specified primary endpoint nor protocol specified statistical methods. According to the reviewer's calculation following the protocol specifications, the p-value is around 0.08. There is also only one randomized study in this submission. However, the current NDA is for the treatment of an extended population (pediatric patients) of juvenile rheumatoid arthritis, and the current compound has been approved for the adult population. Therefore whether the data from the currently submitted study provide sufficient evidence for efficacy in JRA is left for the medical officer to make the final assessment.

/S/

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/S/

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Cc: Archival NDA 21-243
HFD-550/Cook/ Midthun/Johnson
HFD-725/Choi/S.Lin/Huque
HFD-725/Division File/Chron