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APPLICATION NUMBER for: 020182, S006

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical

AUG 26 1999

NDA #: 20-182 / S-006

Applicant: Sigma-tau Pharmaceuticals, Inc.

Name of Drug: Carnitor (levocarnitine) Injection

Indication: For the treatment of manifestations of secondary carnitine deficiency in patients with End Stage Renal Disease.

Documents Reviewed: Volumes 1.1-1.29 dated January 29, 1999 and a volume dated June 23, 1999

This review pertains to the analysis of carnitine levels in two exercise challenge studies: ST-96001 and ST-96002. ST-198-US-96-PK01 is not reviewed here because it is not placebo controlled.

The medical officer for this submission is E. Herman M.D. (HFD-510) with whom this review was discussed.

I. Background

Carnitor has been approved, NDA 20-182, for the acute and chronic treatment of patients with an inborn error of metabolism, which results in secondary carnitine deficiency. This supplement is for the treatment of manifestations of secondary carnitine deficiency in patients with End Stage Renal Disease (ESRD) who require hemodialysis. Hemodialysis removes carnitine from the blood. After months of hemodialysis treatment, patients can manifest low carnitine levels. The sponsor claims that eighty percent of intravenous carnitor usage is for this off label treatment. The sponsor wants to have the indication because some health insurers won't cover this off labeled usage. Carnitor has orphan drug designation for this indication.

In 1988, Kendall-McGraw submitted NDA 19-823 for this indication. The agency did not approve the indication because no clinical benefit was shown for Carnitor for this indication. In particular, no benefit was seen in Study P00835 for plasma lipid profile. Sigma-tau has subsequently acquired the ownership of Carnitor and filed an NDA 20-182, which was approved for treatment of primary systemic carnitine deficiency and also for the acute and chronic treatment of patients with an inborn error of metabolism that results in a secondary carnitine deficiency.

The sponsor conducted two studies ST-96001 and ST-96002 to evaluate whether Carnitor improved exercise tolerance in ESRD patients undergoing dialysis as the primary endpoint. These studies did not show a significant improvement over placebo. The

sponsor has not been able to show clinical benefit for Carnitor in the treatment of ESRD patients undergoing dialysis.

The present submission included a partial reanalysis of study P00835. The reanalysis included analyses on the laboratory measures BUN, creatinine, phosphorus, and hematocrit. Significance was claimed for three of the four laboratory measures: BUN, creatinine and phosphorus. The sponsor stated that BUN, phosphorus, and creatinine changes were not observed in studies ST-96001 or ST-96002. The sponsor attributes this failure to the fact that all of the patients were taking epoetin alfa, which shows increases in these parameters. The sponsor states that most patients on dialysis today receive epoetin alfa. Therefore, the sponsor's statements seem to infer that under the current standard of care, it might be difficult or impossible to show clinical benefit in those parameters. The significance of these post-hoc analyses in 1980's standard of care of dialysis patients is, therefore, not important to a current labeling of the treatment of ESRD patients. In this reviewer's opinion it would be foolish to even discuss the significance of these results from an old study in the label.

This review will only focus upon whether carnitine treatment in ESRD patients with low carnitine level is associated with statistically significant increases in Total Carnitine and L-Carnitine (serum free carnitine) levels. The endpoints were discussed with and agreed upon by the Medical Division.

There was no analysis of carnitine levels in the present submission of Study P00835. The statistical comments of the Oct 20, 1989 letter to the sponsor (Kendall McGaw) stated that because many of the observations for plasma carnitine and RBC carnitine post dialysis were missing, the results of these analyses are unreliable and not useful.

This reviewer in a telephone conversation of June 8, 1999 asked the sponsor to provide SAS data files of the carnitine levels in Study ST-96001 and ST-96002. The sponsor provided these data files in their June 23, 1999 submission. The sponsor provided both original data sets and updated data sets for these studies. The updated data set for Study ST-96001 was needed because of data clarifications for four patients at Week 24 in this study. The update for Study ST-96002 was only for a screening value for one patient, which has no impact on the results presented from that study. The updated results for Study ST-96001 are used in this review.

II. Exercise Tolerance Studies

Studies ST-96001 and ST-96002 were conducted for the purpose of showing clinical benefit for Carnitor in ESRD patients undergoing dialysis. The primary efficacy variable was peak VO_2 after exercise testing. Study ST-96001 studied Carnitor 10 mg, Carnitor 20 mg, and Carnitor 40 mg versus placebo. Study ST-96002 studied Carnitor 20 mg versus placebo.

The tables below give summary statistics of Total Carnitine and L-Carnitine (serum free carnitine) at initial visit and weeks 12 and 24 for Studies ST-96001 and ST-96002.

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This reviewer used a one-way analysis of variance to compare Carnitor dose levels with placebo.

Summary statistics of pre-dialysis plasma concentrations of Total Carnitine in Study ST-96001

Treatment Group		Visit		
		Initial	Week 12	Week 24
Placebo	N	33	32	30
	MEAN	43.23	48.36	47.03
	MEDIAN	40.30	41.80	40.40
	STD	11.79	26.08	22.32
	MIN	20.10	27.40	19.30
	MAX	78.90	172.00	145.00
L-carn 10 mg	N	34	30	28
	MEAN	41.62	184.52	223.39
	MEDIAN	37.90	176.00	209.00
	STD	15.43	102.04	71.65
	MIN	14.10	80.80	111.00
	MAX	81.60	658.00	366.00
L-carn 20mg	N	32	30	28
	MEAN	42.98	320.33	398.96
	MEDIAN	39.75	317.50	374.50
	STD	13.47	86.11	90.57
	MIN	26.80	160.00	231.00
	MAX	77.40	531.00	578.00
L-carn 40 mg	N	34	30	29
	MEAN	42.04	636.20	789.69
	MEDIAN	44.20	649.50	807.00
	STD	12.35	175.48	228.98
	MIN	16.40	235.00	334.00
	MAX	66.70	1200.00	1280.00

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Summary statistics of pre-dialysis plasma concentrations of L-Carnitine (serum free carnitine) in Study ST-96001

Treatment Group		Visit		
		Initial	Week 12	Week 24
Placebo	N	33	32	30
	MEAN	24.43	28.93	27.63
	MEDIAN	23.50	24.65	26.40
	STD	7.02	21.01	11.39
	MIN	14.00	12.80	10.70
	MAX	39.90	132.00	58.00
L-carn 10 mg	N	34	30	28
	MEAN	22.26	115.58	148.36
	MEDIAN	21.70	105.00	147.00
	STD	9.13	69.41	50.45
	MIN	8.00	49.10	75.60
	MAX	51.20	441.00	248.00
L-carn 20mg	N	32	30	28
	MEAN	25.30	209.57	240.32
	MEDIAN	25.50	199.00	236.00
	STD	8.71	56.44	60.42
	MIN	9.31	118.00	120.00
	MAX	49.70	326.00	384.00
L-carn 40 mg	N	34	30	29
	MEAN	24.08	371.13	455.52
	MEDIAN	25.45	368.50	453.00
	STD	8.74	111.34	161.65
	MIN	7.50	124.00	183.00
	MAX	41.80	638.00	770.00

All dose levels of Carnitor were significantly different ($P < 0.001$) from placebo at Weeks 12 and 24 for changes in L-Carnitine (serum free carnitine) levels and Total Carnitine levels.

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Summary statistics of pre-dialysis plasma concentrations of Total Carnitine in Study ST-96002

Treatment Group		Visit		
		Initial	Week 12	Week 24
Placebo	N	30	27	27
	MEAN	42.51	45.77	43.50
	MEDIAN	39.00	43.10	38.20
	STD	14.76	15.41	16.28
	MIN	23.80	15.70	20.00
	MAX	92.00	79.40	80.70
L-Carn 20 mg	N	30	25	23
	MEAN	48.81	321.56	384.31
	MEDIAN	45.95	295.00	364.00
	STD	11.05	126.80	115.55
	MIN	30.60	115.00	190.00
	MAX	74.60	644.00	709.00

Summary statistics of pre-dialysis plasma concentrations of L-Carnitine (serum free carnitine) in Study ST-96002

Treatment Group		Visit		
		Initial	Week 12	Week 24
Placebo	N	30	27	27
	MEAN	23.70	27.05	27.63
	MEDIAN	21.10	25.10	24.50
	STD	8.93	10.51	11.25
	MIN	13.20	10.50	7.78
	MAX	61.90	53.10	54.90
L-Carn 20 mg	N	30	25	23
	MEAN	27.12	189.47	243.43
	MEDIAN	26.70	194.00	237.00
	STD	6.36	69.99	75.84
	MIN	17.50	70.90	107.00
	MAX	41.70	394.00	471.00

Carnitor 20mg was significantly different from placebo ($P < 0.001$) at Weeks 12 and 24 for changes in both L-Carnitine (serum free carnitine) and Total Carnitine levels.

It is apparent from the above tables that Carnitor increases pre-dialysis Total Carnitine and L-Carnitine (serum free carnitine) levels in ESRD patients. This reviewer must leave to medical judgement the decision as to which dose level of Carnitor is appropriate for ESRD patients.

/S/

James R. Gebert, Ph.D.
Mathematical Statistician HFD-715

Concur: Dr. Sahlroot */S/* 8/20/99.

Dr. Nevius *for mull* 8/26/99

This review contains 6 pages of text.

cc:

Orig NDA 20-182/S-006

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HFD-510/Dr. Herman

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