

**Errata to the FDA Briefing Document
Arthritis Advisory Committee Meeting
December 20, 2012**

**NDA 022,151, Ampligen (Poly I:Poly C₁₂U, rintatolimod), Hemispherx for the
treatment of chronic fatigue syndrome**

FDA Errata to the Clinical Review

1. On page 32, third paragraph:

The number and percentage of use of medication both for relief from pain and relief from symptoms of CFS, during the first 4 weeks and the last 4 weeks of the study, were compared.

Should be revised to read (change bolded and underlined):

The number **of days of use** of medication both for relief from pain and relief from symptoms of CFS, during the first 4 weeks and the last 4 weeks of the study, were compared.

2. On page 134, first paragraph:

There are apparent discrepancies in the data submitted by the Applicant in terms of the occurrence and severity of laboratory abnormalities. Specifically, review of the serious adverse event narratives indicates that at least two patients in the controlled studies AMP-502 and 516 had AST and ALT levels greater than 5x ULN and at least one patient had AST or ALT levels >2x ULN and total bilirubin >2x ULN. However, these laboratory values are not represented in Applicant's tables that display laboratory abnormalities in these studies.

Should be revised to read (change bolded and underlined):

There are apparent discrepancies in the data submitted by the Applicant in terms of the occurrence and severity of laboratory abnormalities. Specifically, review of the serious adverse event narratives indicates that at least two **Ampligen-treated** patients in the controlled studies AMP-502 and 516 **had AST levels greater than 5x ULN** and at least one **Ampligen-treated** patient had AST or ALT levels >**3x ULN** and total bilirubin >2x ULN. However, these laboratory values are not represented in Applicant's tables that display laboratory abnormalities in these studies.

3. On page 136, the following paragraph should be added after the third paragraph (change bolded and underlined):

Of note, there are limitations to pooling data. As some patients participated in more than one study, the number of patient participating in pooled studies does not display unique patients.

4. On page 137, paragraph 5

Table 84 displays the Ampligen exposure during the two primary controlled studies and the remainder of the studies in CFS patients.

Should be revised to read (change bolded and underlined):

Table 84 displays the Ampligen exposure during the two primary controlled studies and the remainder of the studies in CFS patients. **Of note, the number of patients enrolled in the predominantly uncontrolled CFS studies and the long-term open label study (Study AMP-511) do not represent unique patients as some patients participated in more than one study. The number of unique patients in these studies is unclear. Thus, examinations of proportions using this denominator are difficult to interpret.**

5. On page 149, Table 94, the correct table should read (change bolded and underlined):

Table 94: Number of patients with AEs of malignancy

	Studies AMP-502 and 516		Other CFS Studies ¹
	Ampligen (N=162) n (%)	Placebo (N=164) n (%)	Ampligen (N=575) n
Patients with neoplasia ²	1 (0.6%)	2 (1.2%)	8
Number of occurrences of AEs of neoplasia ²	1	2	<u>12</u>

1. Includes studies 501 (16 Ampligen), 502T (9 Ampligen, 10 placebo), 502E (34 Ampligen), 504 (10 Ampligen), 509 (152 Ampligen), 516C (190 Ampligen), 511 (164 Ampligen)

Excludes non-melanomatous skin cancer

Source: Adapted from Response to FDA Comment 7 (Module 1.11.3), submitted 11/19/12, table 6, page 2

6. On page 157, Table 101, the correct table should read (change bolded and underlined):

Table 101: Summary of patients with marked liver function tests abnormalities¹ in the 9 submitted Ampligen studies

Study	Treatment	Age/Gender	Narrative summary	Time until event (days)	Possible Hy's law?	SAE according to Applicant?
516	Ampligen	43/M	AST and ALT>25x ULN, total bilirubin>3x ULN	1	Yes	No
504	Ampligen	43/M	GGT elevations, max 676 IU/L, reference range not provided <u>(approximately >9x ULN), other LFTs noted to be normal or slightly elevated</u>	?	Unclear	No
502	Ampligen	39/F	Abdominal pain, SGOT and SGPT elevated >20x ULN, normal bilirubin	36	No	Yes
501	Ampligen	27/F	SGOT 3.8xULN, SGPT >6xULN, normal bilirubin and alk phosphatase 6 hours after infusion	85	No	Yes
<u>502E</u>	<u>Ampligen</u>	<u>37/F</u>	<u>AST >12x ULN and ALT >18x ULN, alk phos slightly elevated (1.1x ULN), normal bilirubin</u>	<u>?</u>	<u>No</u>	<u>No</u>

Hy's Law is defined as ALT≥3x ULN and total bilirubin ≥2x ULN

?=unclear based on information provided

- 1. Marked liver function test abnormalities were defined as AST, ALT, GGT, or total bilirubin >5x ULN**

7. On page 159, Table 102, the correct table should read (change bolded and underlined):

Table 102: Applicant's reports of patients with liver function test elevations in the Ampligen development program

	Controlled Portions of Phase 3 Studies		Predominantly Uncontrolled Portions of Phase 2 and 3 Studies	Long-Term Open Label Study
	Studies 502 and 516		Other CFS studies ¹	Study 511 ²
	Ampligen	Placebo	Ampligen	Ampligen
Number patients treated	162	164	411	141
Laboratory tests of interest	n (%)	n (%)	n (%)	n (%)
Patients with ≥LFT elevation, n (%)	26 (16.0)	12 (7.3)	43 (10.5)	19 (13.5)
SGOT (AST)				
>2x ULN, n (%)	6 (3.7)	4 (2.4)	16 (3.9)	8 (5.7)
>3x ULN, n (%)	0	2 (1.2)	5 (1.2)	2 (1.4)
>5x ULN, n (%)	0	1 (0.6)	3 (0.7)	1 (0.7)
SGPT (ALT)				
>2x ULN, n (%)	20 (12.3)	9 (5.5)	29 (7.1)	7 (5.0)
>3x ULN, n (%)	10 (6.2)	3 (1.8)	14 (3.4)	2 (1.4)
>5x ULN, n (%)	3 (1.9)	2 (1.2)	7 (1.7)	1 (0.7)
Total bilirubin				
>1.5x ULN, n (%)	2 (1.2)	3 (1.8)	8 (1.9)	9 (6.4)
SGOT or SGPT > 3 x ULN and total bilirubin >2X ULN, n (%)	0 (0)	0 (0)	0 (0)	0 (0)

1. Studies 501, 502T, 502E, 504, 509, and 516C; 2. 2. Study AMP-511 at last safety cutoff

Source: Adapted from Response to FDA Comment 9 (Module 1.11.3), submitted 11/19/12, table 8, page 2

8. On page 162, Table 105, the correct table should read (change bolded and underlined):

Table 105: Number of patients with AEs of depression or suicide attempt

	Studies AMP-502 and 516		Other CFS Studies ¹
	Ampligen (N=162) n (%)	Placebo (N=164) n (%)	Ampligen (N=575) n (%)
Patients with AEs of depression or suicide attempt	19 (11.7)	21 (12.8%)	43
Total number of occurrences of AEs of depression or suicide attempt	25	<u>42</u>	62

1. Includes studies 501 (16 Ampligen), 502T (9 Ampligen, 10 placebo), 502E (34 Ampligen), 504 (10 Ampligen), 509 (152 Ampligen), 516C (190 Ampligen), 511 (164 Ampligen)

Source: Response to FDA Comment 7 (Module 1.11.3), submitted 11/19/12, table 6, page 2

9. On page 173, Table 113, the correct table should read (change bolded and underlined):

Table 113: Patients with AEs related to vital sign abnormalities

	Controlled Portions of Phase 3 Studies		Predominantly Uncontrolled Portions of Phase 2 and 3 Studies	Long-Term Open Label Study
	Studies 502 and 516		Other CFS studies ¹	Study 511 ²
	Ampligen	Placebo	Ampligen	Ampligen
Number patients treated	162	164	411	141
Hypertension, n (%)	4 (2.5)	5 (3.0)	6 (1.5)	2 (1.2)
Tachycardia, n (%)	<u>6 (3.7)</u>	5 (3.0)	13 (3.2)	<u>4 (2.4)</u>
Hypotension, n (%)	3 (1.9)	3 (1.8)	8 (1.9)	<u>5 (3.0)</u>
Orthostatic hypotension, n (%)	0 (0)	0 (0)	1 (0.2)	4 (2.4)
Fever, n (%)	32 (19.8)	19 (11.6)	75 (18.2)	45 (27.4)

1. Studies 501, 502T, 502E, 504, 509, and 516C; 2. Study AMP-511 at last safety cutoff

Source: Adapted from Response to FDA Comment 11 (Module 1.11.3), submitted 11/19/12, table 10, page 2