



FDA Arthritis Advisory Committee Meeting December 20, 2012

New Drug Application (NDA) from Hemispherx for rintatolimod (Ampligen) for Chronic Fatigue Syndrome (CFS)

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Center for Drug Evaluation and Research

US Food and Drug Administration

Objectives

- To obtain objective scientific advice and recommendations from outside experts on the New Drug Application (NDA) for Ampligen for the treatment of Chronic Fatigue Syndrome
- To provide public availability of data from the Ampligen program

Chronic Fatigue Syndrome

- Serious, complex, and debilitating disease
- Unknown etiology
- Characterized by profound fatigue >6 months duration; worsened by physical or mental activity
- Multiple body systems affected
- No diagnostic tests
- No approved therapies
- Lack of consensus on nomenclature and disease definition

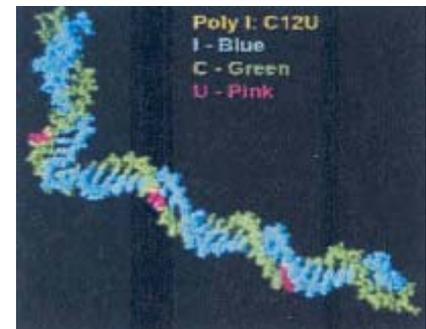


Topics Not Covered in Advisory Committee Meeting

- CFS related
 - Name of disease
 - Diagnostic criteria for disease
 - Optimal endpoints for clinical trials
- Product specific
 - Disciplines other than clinical and statistical (e.g. product quality)

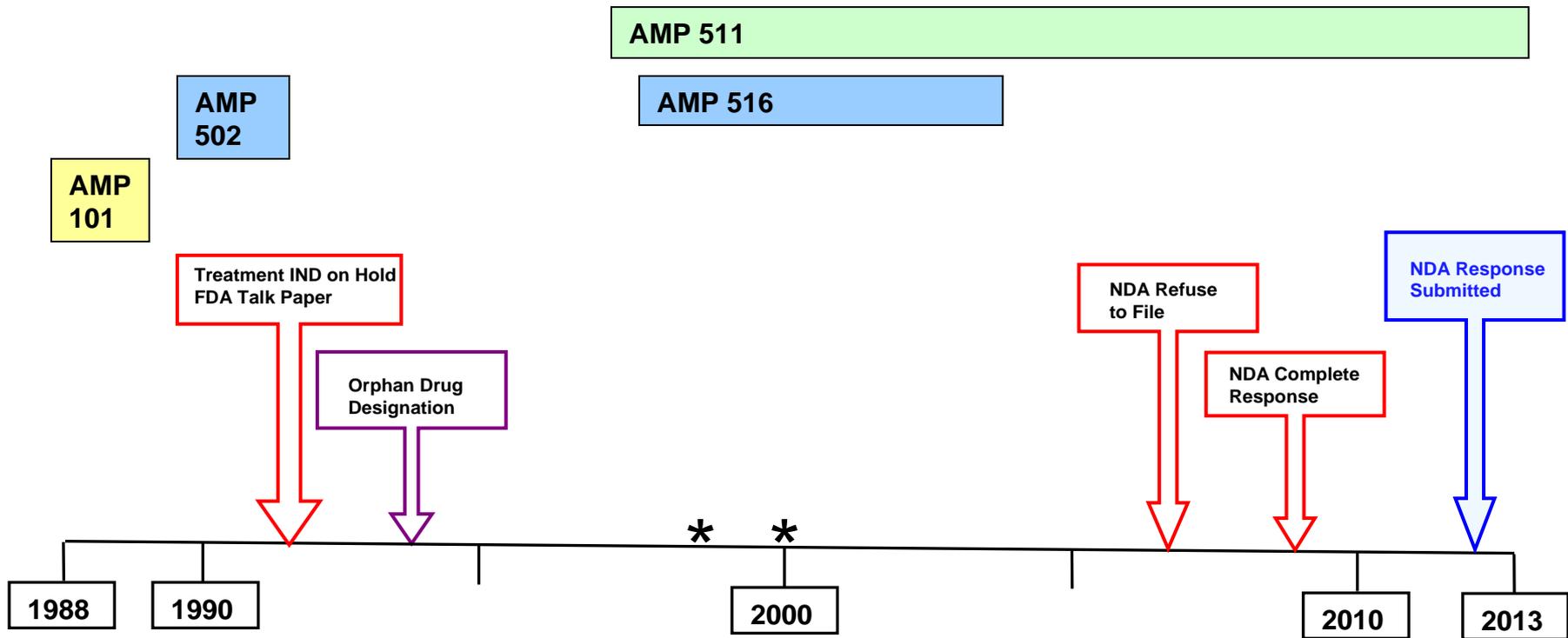
Ampligen

- Nomenclature
 - Ampligen (sponsor's proposed trade name)
 - rintatolimod = Poly I:Poly C₁₂U (established name)
- New molecular entity
- Unknown mechanism of action, ?immune modulator via toll-like receptor 3 → increased interferon production
- Double-stranded RNA → molecular pattern associated with viral infection
- No approved products using dsRNA



Ampligen NDA April 28, 2008,
Figure 2.5.3.F1, Clinical 5
Overview page 5

Development Timeline



*Promotional Violation

Clinical Program Summary

- Initial NDA, submitted October 2007
 - FDA Refusal to File
- Original NDA, submitted April 2008
 - Two placebo-controlled efficacy and safety trials: AMP502 and AMP516
 - Complete response due to lack of evidence of effectiveness or safety
 - Additional data required to support efficacy and safety
- Complete Response, submitted August 2012
 - No new clinical trial data
 - Post-hoc responder and subgroup analyses of AMP516
 - New statistical analysis plans

Primary Controlled Studies in CFS

Study Years conducted	Study design	Test product	N	Duration (weeks)	Primary endpoint
502 <i>1990-1991</i>	R, DB, PC	Ampligen 200mg IV biw x 2 wks, then 400mg IV biw Placebo	45 47	24	KPS
516 <i>1998-2004</i>	R, DB, PC	Ampligen 200mg IV biw x 2 wks, then 400mg IV biw Placebo	117 117	40	ETT duration

Abbreviations: R=randomized, DB=double blind, PC=placebo controlled, biw=twice weekly, KPS=Karnofsky Performance Score, ETT=exercise treadmill test

Issues with Program

- Multiple study conduct issues
 - Related to efficacy
 - Related to adequacy of safety data

Topics for Discussion

- Efficacy data
 - Karnofsky Performance Scale (KPS)
 - Exercise Tolerance Testing (ETT)
 - Other analyses
- Safety data
 - Sufficient to draw conclusions
 - Potential safety concerns



Thank You!

Arthritis Advisory Committee Meeting

Ampligen (Poly I: Poly C₁₂U)

NDA 022,151

Janet Maynard, MD, MHS
Clinical Reviewer

Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
December 20, 2012

Outline

- **Overview of the Clinical Program**

Janet Maynard, MD, MHS

Clinical Reviewer, DPARP, CDER, FDA

- **Statistical Review of Efficacy**

David Hoberman, PhD

Statistical Reviewer, DB II, CDER, FDA

- **Clinical Review of Efficacy, Safety, and Risk/Benefit**

Janet Maynard, MD, MHS

Clinical Reviewer, DPARP, CDER, FDA

Background on Chronic Fatigue Syndrome (CFS)

- **Diagnosis of CFS**

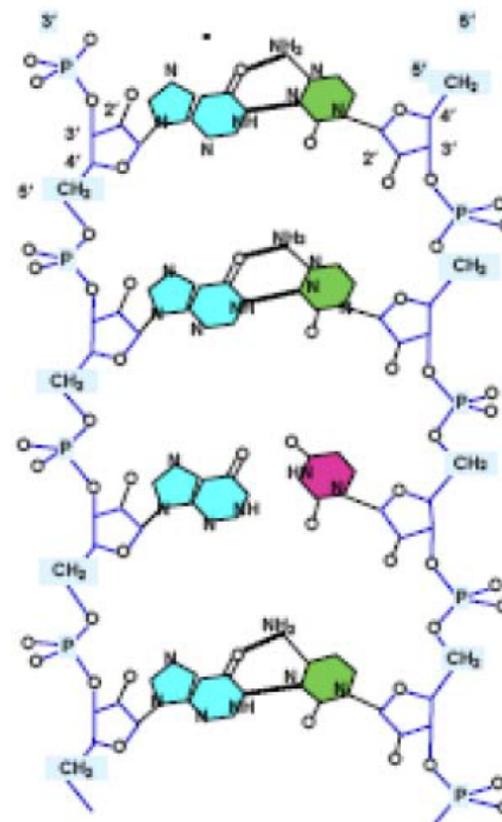
- Unexplained, persistent and relapsing fatigue
- Severe and debilitating disease
- Unknown etiology
- Diagnosis can be difficult
 - Diagnosis of exclusion

- **Management of CFS**

- There is unmet need for CFS patients
- No approved therapy

The Proposed Product: Ampligen

- Ampligen: double-stranded RNA molecule (Poly I:Poly C₁₂U)
- Similar, but distinct, product: Poly I:C
 - Used to mimic models of viral infection in animals
 - Associated with toxicities in humans†
 - Fevers, rigors, hypotension, blood count depression, allergic reactions
- Mechanism of action of Ampligen
 - Unknown
 - Possible activation of toll-like receptors 3
 - Could lead to interferon production



Source: Applicant's proposed label (Module 1.14.1.3), submitted 9/13/12

† J Biol Response Mod. 1985;4:640-9.

Relevant Regulatory History

- AMP-101 performed (1988)
- AMP-502 performed (1990-1)
- Treatment IND placed on clinical hold (1991)
 - Due to unfavorable risk/benefit profile in study AMP-502
- Advisory Committee Meeting (1993)
 - Purpose was to educate the committee about CFS
 - No specific product evaluated
- Cost-recovery study (AMP-511) initiated (1997)
 - Primary study goal: Ampligen safety evaluation
- AMP-516 performed (1998-2004)

Relevant Regulatory History (Continued)

- Pre-New Drug Application (NDA) meeting (8/2006)
 - Make adjustments for multiple comparisons
- NDA submitted; FDA refused to file (10/2007)
 - NDA not sufficiently complete for review due to multiple deficiencies:
 - Lack of dose ranging
 - Missing study reports, laboratory and ECG data, and case report forms
 - Discrepancies in the number of patients in the study reports and the database
 - Statistical analysis plans inconsistent with the protocols
 - Lack of clinical pharmacology data
 - Lack of carcinogenicity data
- NDA resubmitted; Accepted after resolution of some of the issues (7/2008)
 - Complete response issued (11/2009)
- Type A meeting (6/2012)
- NDA resubmitted (8/2012)

Primary Controlled Studies in CFS

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Abbreviations: R=randomized, DB=double blind, PC=placebo controlled, biw=twice weekly, KPS=Karnofsky Performance Score, ETT=exercise treadmill test

- Study conduct issues
- Statistical analysis issues

Other Studies in CFS

Study	Test product	N	Duration
<i>Open-label, uncontrolled studies</i>			
501	AMP 200mg biw, then 100mg QOD [†] , 300mg biw, 400mg biw or 400mg tiw	10	Indefinite
504	AMP 200mg IV biw x 2 wks, then 400mg IV biw	10	Indefinite
509	AMP 200mg IV biw x 2 wks, then 400mg IV biw	152	Up to 3 years
<i>Open-label, uncontrolled extension studies</i>			
502E	AMP 200mg IV biw x 2 wks, then 400mg IV biw	34	≥6 mos
511	AMP 200mg IV biw x 2 wks, then 400mg IV biw	164	Indefinite
516C	AMP 200mg IV biw x 2 wks, then 400mg IV biw	190	24 wks
<i>Controlled studies</i>			
502T	AMP 200mg IV biw x 2 wks, then 400mg IV biw x 2-3 wks, then 400mg IV tiw	9	24 wks
	Placebo	10	

Abbreviations: biw=twice weekly, tiw=three times weekly, R=randomized, DB=double blind, PC=placebo controlled

† No patients received this dose

Overview of Patient Population in Studies AMP-502 and 516

Study	Inclusion Criteria	Exclusion Criteria
502	<ul style="list-style-type: none"> • 1988 CDC case definition of CFS \geq 1 year • Age 18-60 years old • KPS scores 20-60 • Walk on a treadmill at 0% incline at 1 mph (10 seconds) 	<ul style="list-style-type: none"> • Therapy with psychotropic drugs within the last 6 weeks
516	<ul style="list-style-type: none"> • 1988 CDC case definition of CFS \geq 1 year • Negative ANA or negative double stranded DNA, negative RF, and a negative ESR • Laboratory documentation of euthyroid state • Age 18-60 years old • KPS scores 40-60 • Walk on a treadmill at 0% incline at 1 mph (20 seconds) 	<ul style="list-style-type: none"> • Ability to exercise >18 minutes on any baseline ETT test • History of suicidal ideation or attempt within 2 years of baseline • Any past or current diagnosis of major depressive disorder with psychotic or melancholic features, bipolar disorder, schizophrenia, delusional disorders, dementia, anorexia nervosa, or bulimia nervosa

Abbreviations: ANA=anti-nuclear antibody; RF=rheumatoid factor; ESR=erythrocyte sedimentation rate

Concomitant Medications in Studies AMP-502 and 516

Study	Restrictions on Concomitant Medications for Symptoms of CFS
502	<ul style="list-style-type: none"> • Psychotropic drugs were prohibited during the study
516	<ul style="list-style-type: none"> • “Investigators are discouraged from prescribing or recommending the use of any unapproved therapies for CFS/ME”

AMP-502 Study Protocol dated 10/19/90, page 23
AMP-516 Study Protocol dated 4/20/03, page 7

Endpoints in Studies AMP-502 and 516

Study	Duration (weeks)	Primary endpoint	Secondary endpoints
502	24	KPS	<ul style="list-style-type: none"> • ETT duration • ADL • SCL-90-R CD • Signs and symptoms of CFS • Hospitalization/emergency room admissions • Concomitant medications
516	40	ETT duration	<ul style="list-style-type: none"> • KPS • ADL • Signs and symptoms of CFS • Hospitalization/emergency room admissions • Concomitant medications • SF-36 (vitality and general health perceptions)

Abbreviations: KPS=Karnofsky Performance Score, ETT=exercise treadmill test, ADL=activities of daily living, SCL-90-R CD score=Symptoms Checklist 90 Revised Cognitive Deficit Subscale, SF-36=Short Form-36

Evaluation of Safety

Safety Assessments

- Adverse event monitoring
- Vital signs
- Physical examination
- Laboratory tests

Applicant's Definitions

Study	AE definition?	SAE definition?
501	No	No
502	Yes	No
502T	Yes	No
502E	Yes	No
504	No	No
509	Yes	Yes
511	No	No
516	Yes	Yes
516C	Yes	Yes

Abbreviations: AE=adverse event; SAE=serious adverse event

Evaluation of Safety

Safety Assessments

- Adverse event monitoring
- Vital signs
- Physical examination
- Laboratory tests

Applicant's Definitions

Study	AE definition?	SAE definition?
501	No	No
502	Yes	No
502T	Yes	No
502E	Yes	No
504	No	No
509	Yes	Yes
511	No	No
516	Yes	Yes
516C	Yes	Yes

Abbreviations: AE=adverse event; SAE=serious adverse event

Study Conduct Issues: Efficacy

Conduct Issue	Example/Explanation
<p>Major protocol changes during the study</p>	<ul style="list-style-type: none"> –Modification of Bruce ETT protocol during study with subsequent exclusion of these patients from analysis (502) –Unplanned interim analysis with subsequent study discontinuation (502)
<p>Statistical issues</p>	<ul style="list-style-type: none"> –No written analysis plans (502) –Significant changes after study completion (516)
<p>Errors and discrepancies on baseline and week 24 data</p>	<ul style="list-style-type: none"> –Inconsistent baseline data acquisition for KPS (502) –Discrepancies on data listings regarding patient discontinuation (502)
<p>Protocol violations</p>	<ul style="list-style-type: none"> –Enrollment criteria violations (502 & 516) –Use of prohibited medications (502 & 516)

Study Conduct Issues: Safety

Safety reporting concern	Example/Explanation
Inaccuracies in coding of SAEs	FDA identified additional AEs that appeared to meet the definition of SAEs, but were not reported as SAEs
Inconsistencies between Applicant's categorization of AEs with preferred terms and the investigator's verbatim terms	Hospitalizations related to lupus flare were not considered an SAE related to lupus
Omission of certain laboratory values from databases and case report forms	Medical records revealed laboratory values that were not reported in complete study reports and do not appear to be in laboratory databases
Inaccurate descriptions of laboratory values	Laboratory values were described as normal, but review of medical records revealed ongoing abnormalities

Major Considerations

- Concerns regarding study conduct
 - Reliability and adequacy of efficacy data
 - Reliability and adequacy of safety data

Outline

- Overview of the Clinical Program

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Clinical Reviewer, DPARP, CDER, FDA

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Arthritis Advisory Committee Meeting

Ampligen (Poly I: Poly C₁₂U)

NDA 022,151

David Hoberman, PhD
Statistical Reviewer

Office of Biostatistics, Office of Translational Sciences
Center for Drug Evaluation and Research, FDA
December 20, 2012

Outline

- Introductory Comments
- Overview of Efficacy Findings
 - Study AMP-502
 - Study AMP-516
 - Study AMP-516C (Open-label Extension)
- Summary

Introductory Comments

- Post-hoc analyses
- Type 1 error control

Protocol Timelines

Study	Study Date	Relevant Protocol	Date of SAP† (Version 1)	Date of SAP† (Version 1.1)
502	1990 – 1991	10/19/1990	09/18/2007	07/12/2012
516	1998 – 2004	04/20/2003	09/22/2007	07/03/2012

† Statistical Analysis Plan

Analyses – Study AMP-502

- Planned
 - No statistical analysis plan in 1990
- Submitted in 2012
 - KPS: Wilcoxon, Cochran-Armitage tests
 - ETT: ANCOVA on log-transformed baseline, week 24 data

Analyses – Study AMP-516

- Planned
 - ETT: ANCOVA with log-transformed baseline, week 40 data
 - KPS: Fishers Exact test on % with at least 10 point increase
 - Other Quality of Life scales: Wilcoxon test and t-test
- Submitted
 - ETT: ANCOVA on raw data
 - KPS: Wilcoxon or t-tests

Type 1 Error Control

- Multiple secondary endpoints
- Statistical plan essential

Study AMP-502

- Conduct of Study
- Disposition of Subjects
- Overview of Results
 - Primary Endpoint: KPS
 - Secondary Endpoint: ETT
- Summary

Conduct of Study AMP-502

- Unplanned interim analysis
- Effect size
- Unplanned trial curtailment

Conduct of Study AMP-502

- Diversion of subjects after randomization
- ETT protocol change
- Discrepancy in number of dropouts
- Assignment of week 24 values to dropouts

	Ampligen 400 mg	Placebo	Total
Randomized			112
ITT Population	45	47	92
Failed Bruce Protocol	4 (9%)	3 (6%)	7 (8%)
Subject withdrew	4 (9%)	4 (9%)	8 (9%)
Discontinued prior to week 24	15 (33%)	17 (36%)	32 (35%)

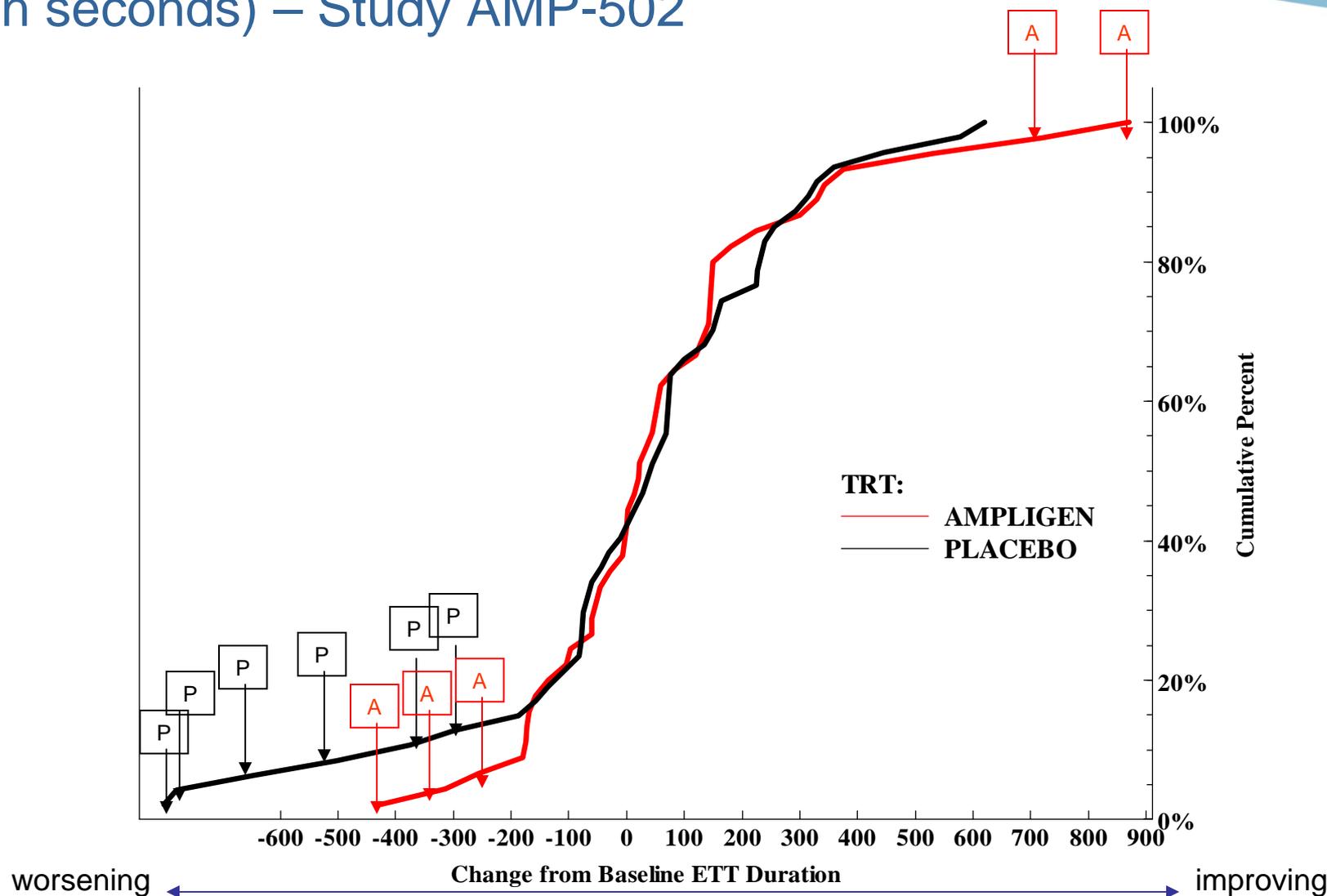
Primary Endpoint: KPS – Study AMP-502

	Ampligen N=45	Placebo N=47	P-value
Baseline median	50	50	
Median change from baseline at Week 24	10	0	
P-value			0.016
Mean change from baseline at Week 24	9.4	3.8	

Secondary Endpoint: ETT (in seconds, arithmetic mean) – Study AMP-502

	Ampligen	Placebo	P-value
ETT (includes all randomized patients)	N=45	N=47	
Baseline mean, seconds	811	672	
Week 24 mean, seconds	874	692	
Mean change from baseline at Week 24	63 (0.18)	20 (0.27)	
FDA's p-value (includes all randomized patients)			0.08
ETT (excludes 7 patients)	N=41	N=44	
Baseline mean, seconds	856	696	
Week 24 mean, seconds	930	713	
Mean change from baseline at Week 24	74	17	
FDA's p-values (excludes 7 patients)	(0.12)	(0.32)	
FDA's and Applicant's p-value (excludes 7 patients)			0.01

Empirical Distribution Function: ETT Duration (in seconds) – Study AMP-502



Summary – Study AMP-502

- Conduct Issues
 - No analysis plan
 - Unplanned interim analysis with effect size followed by curtailment
- Results
 - Post-hoc p-value less than 0.05 for KPS
 - Questionable p-value for ETT
 - o P-value greater than 0.05 for all randomized subjects
 - o Only curve separation among worst ETT changes

Study AMP-516

- Disposition of subjects
- Overview of Results:
 - Primary Endpoint: ETT
 - Secondary Endpoints: KPS & other Quality of Life Measures
 - Subgroups
- Summary

Subject Disposition – Study AMP-516

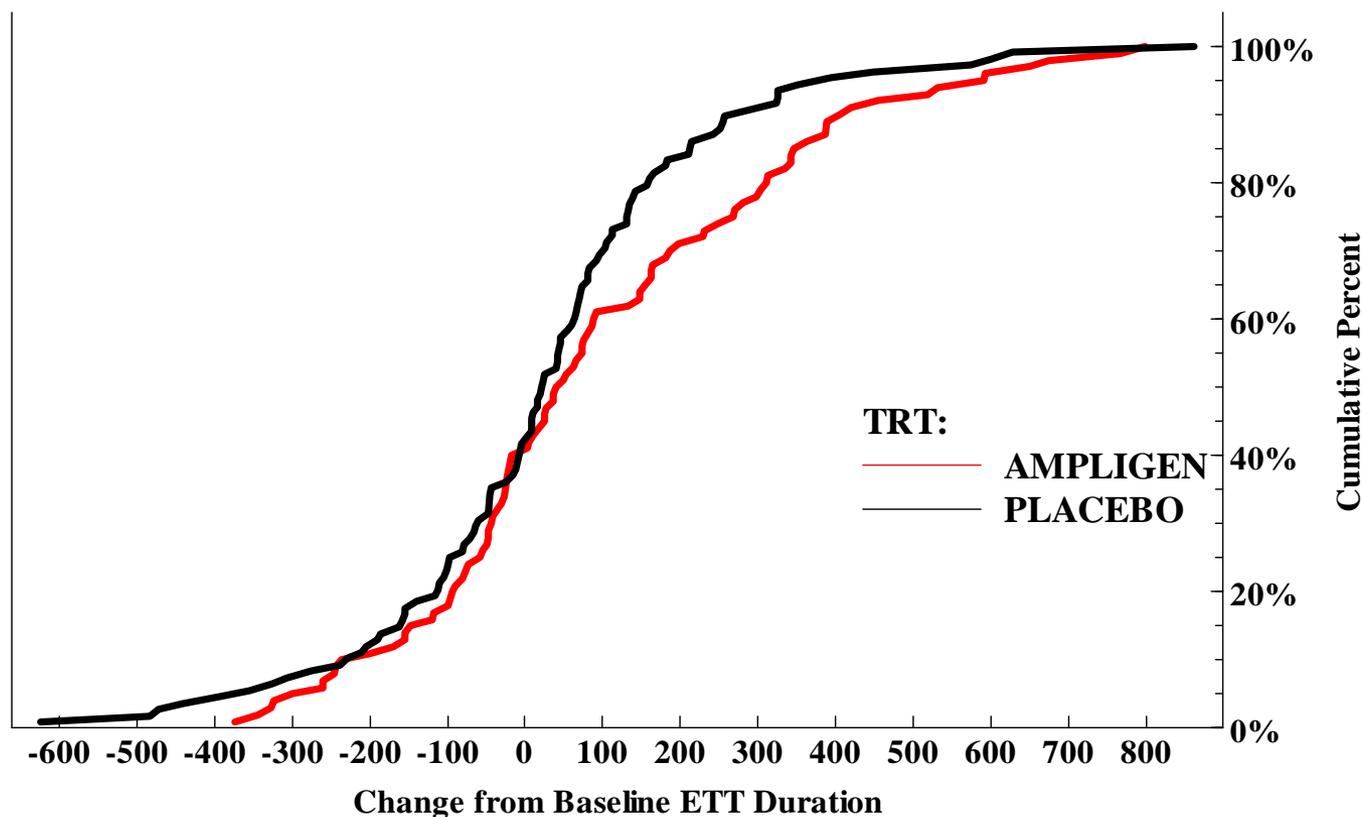
	Ampligen 400 mg	Placebo	Total
Randomized	121	119	240
ITT Population	100	108	208
Subject withdrew†	24 (21%)	16 (14%)	40 (17%)
Missing week 40 data	7 (7%)	7 (6%)	14 (7%)

†Adapted from AMP-516 Study Body Report (Module 5.3.5.1.3), submitted 4/25/08, table 12 (page 50)

Primary Endpoint: ETT Duration (in seconds, arithmetic mean) – Study AMP-516

	Ampligen N=100	Placebo N=108	P-value
ETT (Primary endpoint)			
Baseline mean, seconds	576.6 (257.5)	586.7 (232.1)	
Mean change from baseline at week 40 (SD)	95.7 (251.3)	29.9 (227.3)	
P-values (analysis method)			
Applicant's (untransformed data)			0.047
FDA's p-value (pre-specified primary analysis)			0.10
Median absolute change from baseline, seconds	45	23	

Empirical Distribution Function: ETT Duration (in seconds) – Study AMP-516



worsening ←



→ improving

Efficacy results for dichotomized ETT variables (responder analysis) – Study AMP-516

	Ampligen N=100	Placebo N=108	p-value
At least 20% [†] , n (%)	40 (40)	33 (31)	0.190
At least 25%, n (%)	39 (39)	26 (24)	0.025
At least 50%, n (%)	26 (26)	15 (14)	0.036

[†] protocol-specified

Subgroup Analyses – Study AMP-516

- Repeated analyses
- Correlated p-values
- Purpose of analyses?

Targeted Subgroup – Study AMP-516

- Repeated analysis in 82% of the dataset
- Weak relationship between spontaneous improvement and duration of disease
- Does less than 10 year duration really benefit more?

Quality of Life and Other Patient-Reported Outcomes – Study AMP-516

	P-Value
KPS	0.58
Signs and Symptoms	0.91
Short Form-36 Vitality	0.29
Short Form-36 General Health	0.52
Activities of Daily Living	0.28

Applicant's Analysis on ETT-Quality of Life Correlation (Pooled Placebo and Ampligen Groups) – Study AMP-516

Secondary Endpoint		Dichotomized by ETT improvement		p-value
		<25% (n=144)	≥25% (n=64)	
KPS	Baseline	50.0	50.0	0.017
	Week 40	50.0	60.0	
	Change	0	10.0	
ADL	Baseline	68.3	69.0	0.009
	Week 40	69.4	74.2	
	Change	1.1	5.1	
Vitality	Baseline	11.2	10.6	<0.001
	Week 40	14.6	25.2	
	Change	3.0	14.0	
GHP	Baseline	16.7	18.9	0.031
	Week 40	19.0	23.5	
	Change	2.1	5.2	

†Adapted from Applicant's Briefing Document, 12/20/2012, page 82 Table 6.20

Summary – Study AMP-516

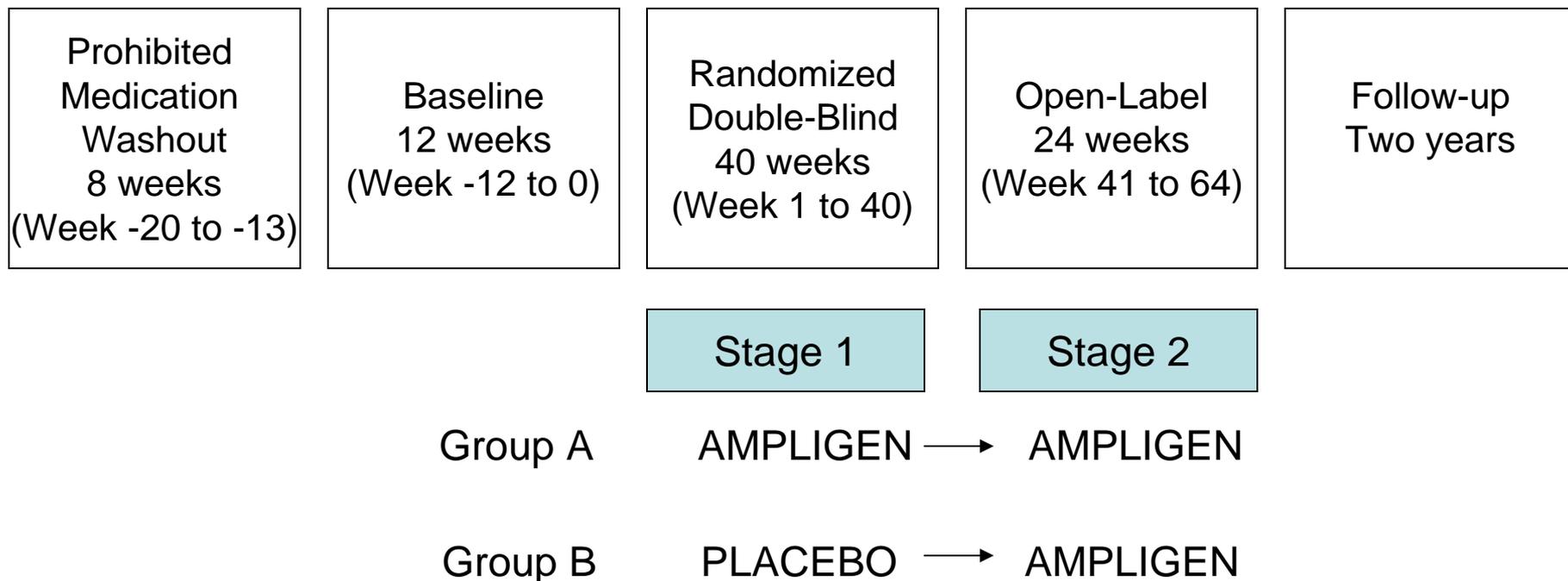
- Pre-specified primary ETT analysis not significant
- Pre-specified 20% responder analysis not significant
- Post-hoc responder analysis p-values below 0.05
- Separation of ETT curves among improvers from baseline

- Non-significant KPS result
- Other QOL not significant

Study AMP-516C (Open-label Extension)

- Study Design
- Overview of FDA Exploratory Analyses Results

Design of Open Label Extension Study AMP-516C



Study AMP-516C – FDA Exploratory Analyses Results

- Within Placebo → Ampligen Sequence
 - 24 weeks on Ampligen vs 20 weeks on placebo
 - Results: $p=0.63$ paired t-test
 $p=0.83$ McNemar test
- Within Ampligen → Ampligen Sequence
 - Durability of response: 16 of 39 (41%) lost 25% responder status
- Between Sequences
 - 64 weeks on Ampligen vs 24 weeks on Ampligen (between sequences)
 - Results: 33% of both cohorts are 25% responders

Outline

- Introductory Comments
- Overview of Efficacy Findings
 - Study 502
 - Study 516
 - Study 516C (Open-label Extension)
- **Summary**

Summary of Efficacy Findings

- ETT
 - Questionable interpretation of p-values in study AMP-502
 - Non-statistical significance in study AMP-516 according to protocol
 - Overlapping ETT curves in study AMP-502 with outliers
 - Separation in ETT curves among improvers in study AMP-516
 - Non-significant result for protocol-specified responder analysis (20% cutoff)
 - P-values below 0.05 for post-hoc responder analyses

Summary of Efficacy Findings (continued)

- KPS
 - Post-hoc p-value less than 0.05 in study AMP-502
 - Mean versus median treatment difference in study AMP-502
 - No statistical evidence of benefit in study AMP-516
- No statistical evidence of efficacy in study AMP-516C

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- **Clinical Review of Efficacy, Safety, and Risk/Benefit**

Janet Maynard, MD, MHS

Clinical Reviewer, DPARP, CDER, FDA

Clinical Review of Efficacy, Safety, and Risk/Benefit

- Efficacy review: clinical implications
- Safety review
 - Background
 - Extent of exposure
 - Main safety results
 - Deaths
 - Nonfatal serious adverse events (SAEs)
 - Common adverse events (AEs)
 - Laboratory abnormalities
- Risk/Benefit

Efficacy Summary

Endpoint	P-value <0.05 According to FDA Analysis?	
	AMP-502 [†]	AMP-516 [‡]
KPS (1° 502)	?	No
ETT (1° 516)	No	No

† Using ITT population

‡ Using protocol pre-specified analysis

- Multiple study conduct and statistical issues
- Secondary quality of life endpoints in AMP-516
 - No demonstration of benefit with Ampligen treatment compared to placebo

Efficacy Summary: Concomitant Medications

- **Applicant's analyses:**
 - Comparison of the number of days medications used for CFS during the first 4 weeks and last 4 weeks of the study
 - Additional post-hoc analyses performed on a subset of medications the Applicant considered to prolong QT
- **Limitations of these analyses:**
 - Use of concomitant medications was prohibited (502) or discouraged (516)
 - Unclear if a standardized protocol used
 - No standardized list of medications for CFS
 - Medications included appear to be for other medical conditions (e.g. anti-dandruff medications)
 - Unclear if number of days of medication use is clinically meaningful

Efficacy Summary: Post-Hoc Analyses

- **Responder analysis**
 - Lacks clinical justification for the response thresholds chosen for CFS patients
 - Not robust across different cut points
 - Not significant at pre-specified response threshold
 - Analyses **pooling treatment groups** are not a measure of efficacy
- **Targeted subgroup analysis**
 - No clear clinical or statistical rationale for the subgroup chosen

Efficacy Review, Safety Review, and Risk/Benefit

- Efficacy review: clinical implications
- Safety review
 - Background
 - Extent of exposure
 - Main safety results
 - Deaths
 - Nonfatal Serious Adverse Events (SAEs)
 - Common adverse events (AEs)
 - Laboratory abnormalities
- Risk/Benefit

Definitions of AEs: CFR and Applicant

CFR† Definitions

- **Adverse Event (AE)**
 - Any untoward medical occurrence
 - Whether or not considered drug related
- **Serious Adverse Event (SAE)**
 - Death
 - Life-threatening adverse event
 - Hospitalization or prolongation of hospitalization
 - Disability/incapacity
 - Congenital anomaly/birth defect

Applicant's Definitions

Study	AE definition?	SAE definition?
501	No	No
502	Yes	No
502T	Yes	No
502E	Yes	No
504	No	No
509	Yes	Yes
511	No	No
516	Yes	Yes
516C	Yes	Yes

† Code of Federal Regulations
21 CFR §312.32(a)

Study Conduct Issues: Safety

Safety reporting concern	Example/Explanation
Inaccuracies in coding of SAEs	FDA identified additional AEs that appeared to meet the definition of SAEs, but were not reported as SAEs
Inconsistencies between Applicant's categorization of AEs with preferred terms and the investigator's verbatim terms	Hospitalizations related to lupus flare were not considered an SAE related to lupus
Omission of certain laboratory values from databases and case report forms	Medical records revealed laboratory values that were not reported in complete study reports and do not appear to be in laboratory databases
Inaccurate descriptions of laboratory values	Laboratory values were described as normal, but review of medical records revealed ongoing abnormalities

Extent of Exposure in CFS and Limitations in Safety Analyses

Ampligen Exposure in CFS

Treatment duration	Ampligen n
Overall exposure	565 [†] [589 ^{?‡}]
6 months	385 [†]
1 year	170 [†] [about 100 ^{?‡}]

[†] NDA submission, 4/25/08, page 33

[‡] Applicant's briefing materials for 12/20/12 AAC meeting, page 90

Limitations in Safety Analyses

- Uncertainties in exposure
- Consideration of unique patients
 - Patients in more than one study are counted multiple times when studies are pooled
- Periods of drug discontinuation
- Heterogeneous studies
- Studies of longer duration selected patients who were tolerating Ampligen

Extent of Exposure by Study Design

	Studies AMP-502 and 516		Other CFS Studies [†]
	Ampligen N=162	Placebo N=164	Ampligen N=[575]

† 501, 502T, 502E, 504, 509, 511, 516C

Source: Adapted from Response to FDA comment 3 (Module 1.11), submitted 11/19/12, page 2

- **The number of patients in the other CFS studies does not represent unique patients as some patients participated in multiple studies**

Death

	Studies AMP-502 and 516		Other CFS Studies [†]
	Ampligen N=162	Placebo N=164	Ampligen N=[575]
Death, n	0	0	3
FDA's assessment			<ul style="list-style-type: none"> • Acute respiratory failure in the setting of pneumonia, sepsis, interstitial fibrosis, and pulmonary embolus • Suicide • Suicide

[†] 501, 502T, 502E, 504, 509, 511, 516C; these are not unique patients as some patients participated in multiple studies

Comparison of SAEs Identified by Applicant and FDA

Study	SAEs reported by Applicant	SAEs identified by FDA [†]
502	14 [‡]	[35]
511	22 [§]	[49]
516	24	[48]

- FDA identified adverse events coded as requiring hospitalization as SAEs
 - This excluded other factors that are part of the SAE definition
- Sponsor noted that some patients coded as requiring hospitalization were seen in the ER or hospitalized for short stays

† Adverse events coded as hospitalization were identified as SAEs by the FDA
 ‡ AMP-502 Complete Study Report (Module 5.3.5.1.3), submitted 4/25/08, page 72
 § AMP-511 Safety Report (Module 5.3.5.2.3), submitted 8/1/12, page 12
 || AMP-516 Complete Study Report (Module 5.3.5.1), submitted 4/25/08, page 99

Applicant's Reports of Nonfatal SAEs

	Study AMP-502 [†]		Study AMP-516 [§]	
	Ampligen N=45	Placebo N=47	Ampligen N=117	Placebo N=117
Patients with SAEs, n (%)	3 (6.7)	[5] [‡] (10.6)	12 (10.3)	6 (5.1)
Number of SAEs	4	[8] [‡]	16	8

[†] AMP-502 Complete Study Report (Module 5.3.5.1.3), submitted 4/25/08, page 66

[‡] Recorded as 6 patients experiencing 10 SAEs on page 72

[§] AMP-516 Complete Study Report (Module 5.3.5.1), submitted 4/25/08, page 99

- For Study AMP-502, numbers do not include SAEs occurring on study drug after 24 weeks

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Nonfatal SAEs of Interest

- FDA reviewed all SAE narratives and identified potential safety concerns:
 - Thrombosis
 - Major cardiac events
 - Malignancy
 - Acute macular neuroretinopathy
 - Infusion reactions
 - Abdominal pain
 - Liver function test abnormalities
 - Neuropsychiatric events
 - Infections
 - Autoimmune disease

Context of Nonfatal SAEs of Interest

- **Importance**
 - Clinically severe
 - Rare
- Animal data revealed similar toxicities findings
- **Limitations**
 - Unique patients
 - Imbalances in treatment exposure
 - Duration
 - Ampligen
 - Safety analysis limited to SAE narratives provided by Applicant

SAEs Related to Thrombosis

	Studies AMP-502 and 516		Other CFS Studies†
	Ampligen N=162	Placebo N=164	Ampligen N=[575]
Thrombosis, n	1	0	2
Applicant's preferred term (FDA's assessment)	<ul style="list-style-type: none"> Pulmonary embolus 		<ul style="list-style-type: none"> Cardiovascular disorder (Superior vena cava thrombosis) Peripheral edema (Deep venous thrombosis, pulmonary embolus)

† 501, 502T, 502E, 504, 509, 511, 516C; these are not unique patients as some patients participated in multiple studies

SAEs Related to Major Cardiac Events

	Studies AMP-502 and 516		Other CFS Studies ¹
	Ampligen N=162	Placebo N=164	Ampligen N=[575]
Major cardiac events, n	1	0	2
Applicant's Preferred term (FDA's assessment)	<ul style="list-style-type: none"> • Cerebrovascular accident 		<ul style="list-style-type: none"> • Cerebrovascular accident • Chest pain (Myocardial infarction)

† 501, 502T, 502E, 504, 509, 511, 516C; these are not unique patients as some patients participated in multiple studies

SAEs Related to Malignancy

	Studies AMP-502 and 516		Other CFS Studies [†]
	Ampligen N=162	Placebo N=164	Ampligen N=[575]
Malignancy, n	0	0	1
Applicant's Preferred term			Breast neoplasm

[†] 501, 502T, 502E, 504, 509, 511, 516C; these are not unique patients as some patients participated in multiple studies

Applicant's Reports of AEs Related to Malignancy

	Studies AMP-502 and 516		Other CFS Studies [†]
	Ampligen N=162	Placebo N=164	Ampligen N=[575]
Patients with malignancy, n	1	2	8
Number of occurrences of malignancy	1	2	12

[†] 501, 502T, 502E, 504, 509, 511, 516C; these are not unique patients as some patients participated in multiple studies

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

SAE Related to Acute Macular Neuroretinopathy

	Studies AMP-502 and 516		Other CFS Studies [†]
	Ampligen N=162	Placebo N=164	Ampligen N=[575]
Acute macular neuroretinopathy, n	0	0	1
Applicant's Preferred term			Retinal disorder

† 501, 502T, 502E, 504, 509, 511, 516C; these are not unique patients as some patients participated in multiple studies

- Very rare
 - 41 cases reported in English-language medical literature
 - Unclear etiology
 - 44% cases associated with influenza-like syndrome prior to the event
- Produces transient or permanent visual impairment

SAEs Related to Possible Infusion Reactions

	Studies AMP-502 and 516		Other CFS Studies [†]
	Ampligen N=162	Placebo N=164	Ampligen N=[575]
Infusion reactions, n	0	0	2
Applicant's preferred term (FDA's assessment)			<ul style="list-style-type: none"> • Syncopal episode (Infusion reaction) • Chills (Infusion reaction)

† 501, 502T, 502E, 504, 509, 511, 516C; these are not unique patients as some patients participated in multiple studies

SAEs Related to Abdominal Pain

	Studies AMP-502 and 516		Other CFS Studies [†]
	Ampligen N=162	Placebo N=164	Ampligen N=[575]
Abdominal pain, n	5	3	6

† 501, 502T, 502E, 504, 509, 511, 516C; these are not unique patients as some patients participated in multiple studies
There was also one event in the placebo group of the Other CFS Studies

Patients with Marked Liver Function Abnormalities[†] in the Ampligen CFS Studies

Study	Treatment	Elevation Above Upper Limit of Normal				Possible Hy's law [‡] ?
		AST	ALT	Total bilirubin	GGT	
516	Ampligen	>25x	>25x	>3x	--	Yes
504	Ampligen	?	?	?	>9x	Unclear
502	Ampligen	>25x	>25x	Normal	--	No
501	Ampligen	>3x	>6x	Normal	--	No
502E	Ampligen	>12x	>18x	Normal	--	No

[†] AST, ALT, GGT, or total bilirubin >5X ULN

[‡] Hy's Law: ALT or AST ≥3x ULN and total bilirubin ≥2x ULN; FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009

Comparison of Applicant's and FDA's Identification of Liver Function Test Elevations

	Studies AMP-502 and 516	
	Ampligen (N=162)	
	Sponsor Reported n	Identified in FDA Review of Narratives n
AST		
>5x ULN	0	2
AST or ALT >3x ULN and total bilirubin >2X ULN	0	1

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

SAEs Related to Neuropsychiatric Events

	Studies AMP-502 and 516		Other CFS Studies†
	Ampligen N=162	Placebo N=164	Ampligen N=[575]
Neuropsychiatric event, n	4	3	5
Applicant's preferred term (FDA's assessment)	<ul style="list-style-type: none"> • Flu syndrome (Encephalopathy) • Depression • Depression; Anxiety • Suicide attempt 	<ul style="list-style-type: none"> • Depression • Depression • Anxiety; Depression 	<ul style="list-style-type: none"> • Depression (Attempted suicide) • Encephalopathy • Overdose (Attempted suicide) • Tremor (Bipolar disorder) • Overdose (Attempted suicide)

† 501, 502T, 502E, 504, 509, 511, 516C; these are not unique patients as some patients participated in multiple studies

- In addition, 2 Ampligen-treated patients died secondary to suicide

SAEs Related to Infection

	Studies AMP-502 and 516		Other CFS Studies†
	Ampligen N=162	Placebo N=164	Ampligen N=[575]
Infection, n	4	0	6
Applicant's preferred term (FDA's assessment)	<ul style="list-style-type: none"> • Urinary tract infection • Pneumonia • Infection • Abscess 		<ul style="list-style-type: none"> • Infection (Sepsis) • Pneumonia • Sepsis (Xanthomonus maltophilia sepsis) • Unclear (Sinusitis) • Diarrhea (Clostridium difficile colitis) • Bronchitis

† 501, 502T, 502E, 504, 509, 511, 516C; these are not unique patients as some patients participated in multiple studies

- In addition, 1 Ampligen-treated patients died secondary to sepsis

SAEs Related to Autoimmune Disease

	Studies AMP-502 and 516		Other CFS Studies [†]
	Ampligen N=162	Placebo N=164	Ampligen N=[575]
Autoimmune disease, n	0	0	2
Applicant's preferred term (FDA's assessment)			<ul style="list-style-type: none"> • Back pain (Lupus flare) • Pain; fever; sepsis (Lupus flares x 2)

† 501, 502T, 502E, 504, 509, 511, 516C; these are not unique patients as some patients participated in multiple studies

Common AEs

- Events >5% of patients and more frequently in Ampligen than placebo in Studies AMP-502 and 516:
 - Flu syndrome
 - Headache
 - Fever
 - Pain
 - Pruritus
 - Diarrhea
- In AMP-516, the following AEs were more frequent in the Ampligen than placebo group ($p < 0.05$):
 - Flu syndrome
 - Chills
 - Vasodilatation
 - Dyspnea

Applicant's Reports of Laboratory Abnormalities

	Studies AMP-502 and 516		Other CFS Studies [†]
	Ampligen (N=162) n (%)	Placebo (N=164) n (%)	Ampligen (N=575) n
Liver function test elevation	26 (16.0)	12 (7.3)	62
Hematocrit<32 or hemoglobin<11	15 (9.3)	10 (6.1)	45
WBC<4,000	49 (30.2)	47 (28.7)	165
Creatinine>1.5	3 (1.9)	1 (0.6)	8

† 501, 502T, 502E, 504, 509, 511, 516C; these are not unique patients as some patients participated in multiple studies

- Of note, laboratory studies were not performed at a central facility
- These are the results reported by the Applicant, not obtained from medical records

Source: Adapted from Response to FDA Comment 10 (Module 1.11.3), submitted 11/19/12, table 9, page 2-3 and Response to FDA Comment 9 (Module 1.11.3), table 8, page 2

Safety summary

- Extent of exposure
- Reliability
- Safety signals

Efficacy Review, Safety Review, and Risk/Benefit

- Efficacy review: clinical implications
- Safety review
 - Background
 - Extent of exposure
 - Main safety results
 - Deaths
 - Non-fatal Serious Adverse Events (SAEs)
 - Common adverse events
 - Laboratory abnormalities
- **Risk/Benefit**

Context for Risk/Benefit Assessment

- CFS is a severe and potentially debilitating disease
- There is unmet need for CFS patients
- For approval: efficacy and safety must be defined

Benefit/Risk Assessment

- Benefit
 - AMP-502: questionable trend for KPS
 - However, numerous study conduct issues and study stopped early
 - No replication of results
 - Lack of support from protocol-specified analyses for ETT
 - Unclear clinical rationale for proposed post-hoc analyses
- Risk
 - Concerns regarding adequacy and reliability of safety database
 - Potential serious safety signals



FDA Arthritis Advisory Committee Meeting December 20, 2012

New Drug Application (NDA) from Hemispherx for rintatolimod (Ampligen) for Chronic Fatigue Syndrome (CFS)

Theresa M. Michele, MD

Clinical Team Leader, Division of Pulmonary, Allergy,
and Rheumatology Products

Center for Drug Evaluation and Research
US Food and Drug Administration

Public Testimony

- Enormous public interest in meeting
 - Many patients and advocates in attendance
 - Many more attending via webcast
 - Public testimony
 - 30+ registered speakers
 - 700+ written statements
- FDA actions on CFS drug development
 - <http://www.fda.gov/Drugs/NewsEvents/ucm319188.htm>

Topics for Discussion

- Efficacy data
 - Karnofsky Performance Scale (KPS)
 - Exercise Tolerance Testing (ETT)
 - Other analyses
- Safety data
 - Adequate to draw conclusions
 - Potential safety concerns

Approval of an Application - 21 CFR 314.105 (c)

“FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling”

Efficacy Standard

- 21 CFR 314.125 Refusal to Approve an Application

(b) (5) "... substantial evidence consisting of adequate and well-controlled investigations ... that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."

Safety Standard

- 21 CFR 314.125 Refusal to Approve an Application

(b) (2) “... do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.”

(b) (3) “The results of the test show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions.”

(b) (4) “There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.”

Risk-Benefit

- Considered in context of serious disease with no approved therapies
- Use clinical judgment regarding acceptable risks for given benefit
- Still need substantial evidence of efficacy and evaluable safety profile
- Evidence standard same for all approval pathways, including orphan diseases

Question 1

Discussion

Discuss the efficacy data for Ampligen considering the following:

- a) Karnofsky performance scale (KPS)
- b) Exercise tolerance testing (ETT)
- c) Other analyses (e.g. quality of life, concomitant medication use)



Question 2

Discussion

Discuss the safety data for Ampligen.

Question 3

Voting and Discussion

Considering the totality of the data, is there substantial evidence of efficacy for Ampligen for the treatment of patients with chronic fatigue syndrome (CFS)? **(Voting question)**

- a) If not, what further data should be obtained? (Discuss)

Question 4

Voting and Discussion

Has the safety of Ampligen been adequately assessed and characterized for the treatment of chronic fatigue syndrome (CFS)? **(Voting question)**

- a) If not, what further data should be obtained? (Discuss)

Question 5

Voting and Discussion

Is the safety profile of Ampligen adequate for approval for the treatment of CFS?

(Voting question)

- a) If not, what further data should be obtained? (Discuss)

Question 6

Voting and Discussion

Based on the information included in the briefing materials and presentations, has the applicant provided sufficient efficacy and safety data to support marketing of Ampligen for the treatment of chronic fatigue syndrome (CFS)? **(Voting question)**

- a) If not, what further data should be obtained?
(Discuss)