

Ampligen[®] for the Treatment of Chronic Fatigue Syndrome

**rintatolimod (Poly I: Poly C₁₂U)
NDA 22-151**

**Hemispherx Biopharma, Inc.
Arthritis Advisory Committee
December 20, 2012**

Introduction

**William A. Carter, M.D.
Chief Executive Officer and
Chief Scientific Officer,
Hemispherx Biopharma, Inc.**

Chronic Fatigue Syndrome (CFS)

- Severely debilitating progressive disease
- Effects multiple organ systems
 - >1 million diagnosed cases in U.S.
 - ~10-20% severely afflicted (~150,000)
- CDC finds to be as debilitating as MS, SLE, RA
- No approved therapies
- Substantial unmet medical need

Ampligen

- Developed as a highly selective inducer of interferon
- Selectively targets toll-like receptor 3 (TLR-3)
- Synthetic double-stranded RNA (dsRNA)
- Activates innate immune pathway
- Not immunosuppressive

Agenda

Introduction

William A. Carter, M.D.
Christopher Snell, Ph.D.

Unmet Medical Need

Lucinda Bateman, M.D.

Scientific Rationale

William A. Carter, M.D.

Safety

David R. Strayer, M.D.

Efficacy

David R. Strayer, M.D.

Richard P. Chiacchierini, Ph.D.

Benefit Risk

William A. Carter, M.D.
Lucinda Bateman, M.D.

Unmet Medical Need

Dr. Lucinda Bateman

**Director of the Fatigue Consultation Clinic;
Adjunct Instructor, University of Utah,
Family and Preventive Medicine, and
Anesthesia; Executive Director, OFFER
(Organization for Fatigue and Fibromyalgia
Education and Research); Salt Lake City, UT**

CFS Historical Background

- A paper first using the term “CFS” was published in 1988 (Holmes) to replace the misnomer “Chronic EBV” but still described a post-infection or post-viral syndrome
- CFS is known by other names:
 - CFIDS- Chronic Fatigue and Immune Dysfunction Syndrome
 - ME - Myalgic Encephalomyelitis (or Encephalopathy)
 - Post-Viral or Post-Infectious Fatigue Syndrome
 - Chronic Epstein-Barr Syndrome, Chronic EBV, etc.
- CFS is not a new illness. CFS is world-wide and multicultural

CFS Epidemiology

- **More common in women**, but impacts men, children and adolescents
- A debilitating, illness increases mortality (*debilitation equal to RA, MS*)
- Most ill >5 years
- More common yet less recognized in racial/ethnic minorities and in socioeconomically disadvantaged

1994 CFS Case Definition, CDC Definition

- Clinically evaluated, unexplained, persistent or relapsing fatigue of at least 6 months duration, that is *of new or definite onset...* and results in substantial reduction in previous levels of activity, plus...
- The concurrent occurrence of at least 4 of the following 8 symptoms:
 - post-exertional malaise
 - impairment in short-term memory or concentration
 - unrefreshing sleep
 - muscle pain
 - multi-joint pain
 - headaches
 - sore throat
 - tender cervical or axillary lymph nodes

Management of ME/CFS

Currently supportive and symptomatic

There are no drugs with an FDA treatment indication for CFS

General Principles of Supportive Management: CFS Standard of Care

- **Address all chronic medical issues**
- **Prioritize and treat disabling symptoms⁺, but economize medications**
- **Prevent deconditioning**

+ The concomitant medication usage is specifically to palliate certain severe symptoms of CFS

Prioritize and Manage Disabling Symptoms⁺

- **Deconditioning and post exertional malaise**
- **Fatigue and cognitive complaints**
- Pain, headaches
- Sleep disturbances
- Orthostatic intolerance
- Grief, despair and chronic illness adaptation

⁺ Ampligen treatment specifically decreased the use of concomitant medications otherwise needed to palliate CFS symptoms

Fatigue “Treatments”: None are FDA Approved for CFS, Benefits are Modest and Transitory

- bupropion 100-300 mg each AM
- *modafinil* 50-400 mg. Long acting. *Indicated for narcolepsy, obstructive sleep apnea and shift work sleep disorder.*
- *amphet/dextroamphet* 5-30 mg bid-tid.
Schedule II. Short acting or XR.
- *methylphenidate* 5-20 mg 2-3x per day.
Schedule II. Short acting or SR.



**Gene Expression Studies in CFS
Following Exercise as a Stressor
Demonstrate Post Exertional
Malaise (PEM)**

University of Utah

Chronic Fatigue Syndrome

- After moderate exercise 71% of CFS patients had marked increases in sensory, adrenergic, and cytokine receptors compared to sedentary controls
- These post-exercise gene expression changes correlated with behavioral measures of fatigue and pain

Main Causes of Death in Patients with Chronic Fatigue Syndrome

Cause of Death	Number (%) of Subjects n=144	Percent	
		Male	Female
Heart failure ¹	29 (20.1%)	34.5	65.5
Suicide ¹	29 (20.1%)	17.2	82.8
Cancer	28 (19.4%)	17.9	82.1

¹ Statistically significant at $p < 0.01$

Data source: Jason LA, et al. *Health Care Women Intl.* 2006

The CFS Population Experienced Premature Death Compared to the US Population

	Age of Death CFS	Age of Death US Population
Cancer	48	72
Suicide	39	48
Heart Failure	59	83

Hypothesis: early deaths are in the 15% of CFS population which are severely debilitated. Jason study is consistent with age of the populations studied in Ampligen program

Serious Medical Need

- CDC studies have shown that CFS can be as debilitating as multiple sclerosis, lupus, and rheumatoid arthritis
- The CDC states that CFS affects approximately 1,000,000 people in the US and that the disease results in over \$14 billion in healthcare costs and \$9 billion in lost productivity each year. Between 14% to 15% of the total CFS population, approximately 150,000, are severely debilitated
- Same CFS patient population as Ampligen clinical program
- **My clinical involvement with Ampligen began in year 2003 and continues to present**

Serious Medical Need - continued

I believe the quality of life in ME/CFS cannot be improved without specific treatment for profound fatigue. Evidence exists that secondary quality of life issues significantly improve when core symptom, profound fatigue, is relieved. SF-36, a validated self-reporting instrument in CFS, can measure the quality of life improvements which occur when the profound fatigue is relieved and physical activity improves

Gaining Clinical Perspective on CFS

Dr. Nancy Klimas in the **NY Times**, 2009: “*My H.I.V. patients for the most part are hale and hearty thanks to three decades of intense and excellent research and billions of dollars invested. Many of my C.F.S. patients, on the other hand, are terribly ill and unable to work or participate in the care of their families. I split my clinical time between the two illnesses, **and I can tell you if I had to choose between the two illnesses I would rather have H.I.V.***” [italics added for emphasis]

Professor of Medicine and Chair of the Department of Clinical Immunology; Principal investigator, National Institutes of Health sponsored CFS Research Centers; Former President of the International Association of CFS/ME; Principal Investigator on AMP Treatment Protocol since 2011; Authored over 150 scientific articles, 18 book chapters; Board Certified in internal medicine and diagnostic laboratory immunology

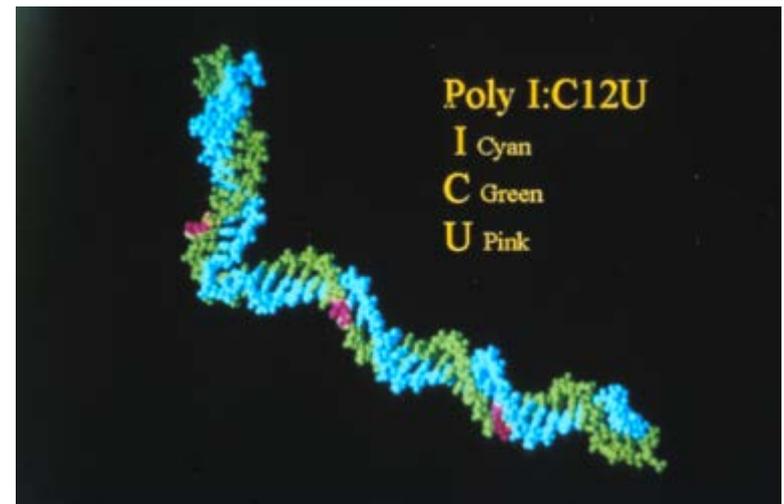
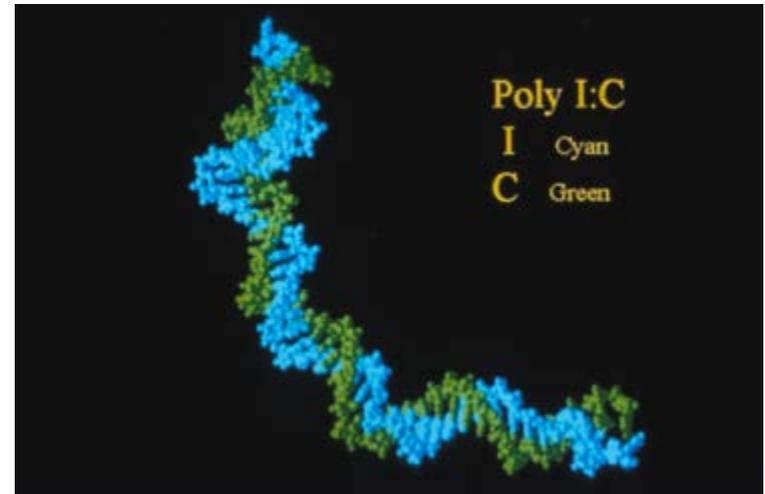
The reality is the risks associated with CFS far outweigh any perceived risks associated with Ampligen. A person left untreated will face a life of progressive debilitation and premature death

Scientific Research

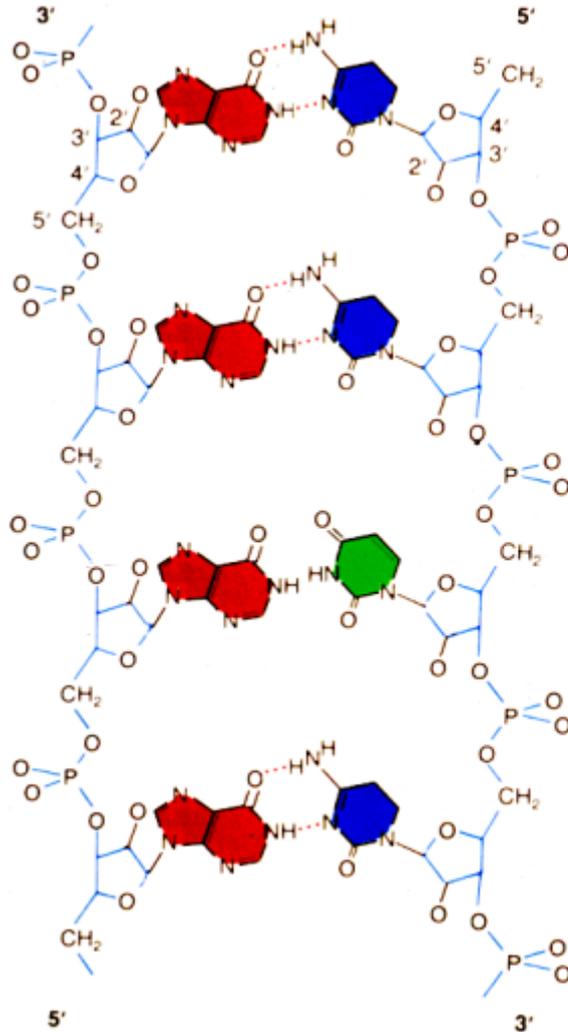
**William A. Carter, M.D.
Chief Executive Officer and
Chief Scientific Officer,
Hemispherx Biopharma, Inc.**

Molecular Models: Ampligen vs. Congeners

- Introduction of uridine into the poly C strand provides a localized instability in the complex observed by circular dichroism (CD) with melting studies of Ampligen vs. poly (I) : poly (C)
- Instability allows hydrolytic site access by serum RNAses with sharp reduction in blood $\frac{1}{2}$ life
- **Reduction in Ampligen $\frac{1}{2}$ life correlated with marked reduction in primate toxicity and immunotoxicity**
- Ampligen is a **selective⁺ TLR3 agonist** compared to poly (I) : poly (C) which is non-selective⁺



Ampligen (Poly I : Poly C₁₂U) Structure

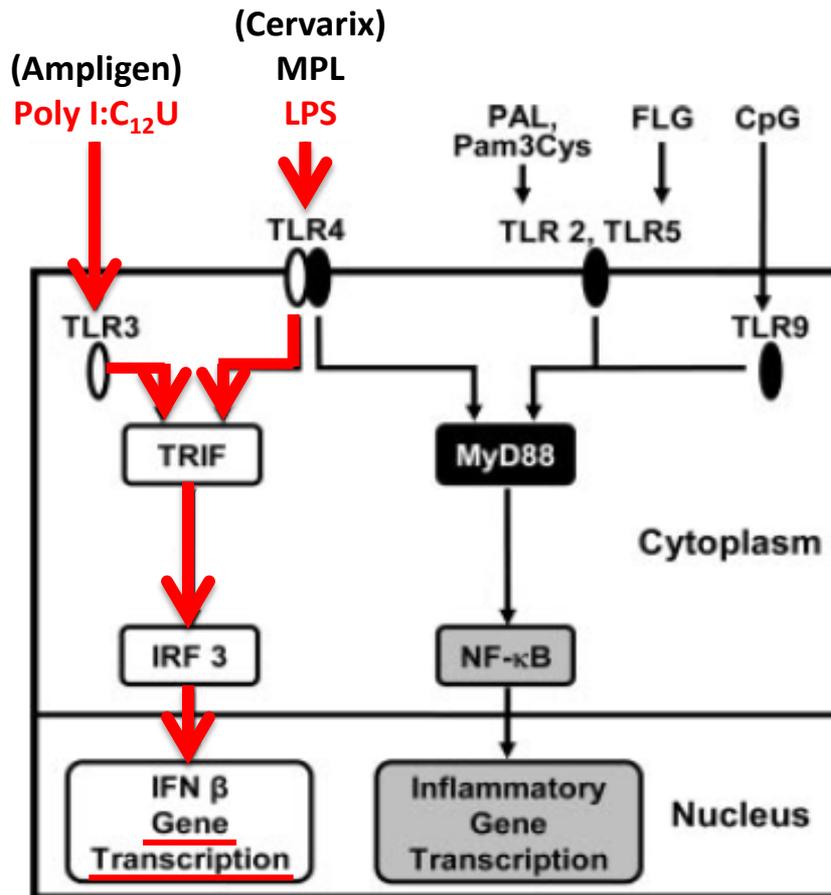


- dsRNA consisting of one strand of the homopolymer, poly I annealed with a heteropolymer, polyC₁₂U
- Rapidly hydrolyzed by plasma RNase

Summary: Safety Aspects of Ampligen

- Ampligen degradation in blood is mediated by enzymes yielding completely natural degradation products (ribonucleotides)
- Half-life is less than 40 minutes
- **No evidence of any cumulative clinical toxicities in >600 patient years of Ampligen exposure**
- **Safety profile exceeds multiple FDA Guidance requirements regarding**
 - a) overall drug exposure**
 - b) liver safety**
 - c) immune profiles of recently approved immunomodulator given to healthy children to protect against a disease (HPV) they may never encounter**

Mechanism of Action of Ampligen as a TLR-3 Agonist is Shared in Part with TLR-4 Agonists



- A TLR-4 agonist, LPS derivative, has been FDA approved as a component of a HPV vaccine (Cervarix[®]) to prevent infection by certain serotypes of oncogenic HPV in healthy females age 9-25 years

Analysis Today Incorporates Five FDA Review Divisions

- **FDA Advisory Committee (Antiviral) convened to approve Phase III protocol design**
- **Program Data Safety Monitoring Board. Recommendation issued**
- **Treatment IND Authorization (Dr. Woodcock, CDER)**
- **Multiple review Divisions within FDA.** Unusual. Most products have same review Division during their entire development. **Guidance from five (5) different Divisions diverged/conflicting advice** on major points, such as: interpreting **primary endpoints** (method of analysis), its collection and analysis, and different thresholds for determining toxicity and safety
- In contrast, Hemispherx has had the **same medical monitor for more than 20 years (Dr. David Strayer)**

Multiple Different FDA Review Divisions During Clinical Development: Gaps in Continuity of Dialogue Occurred

FDA Division	BIOLOGICS	→	ANTI-VIRAL	→	SPECIAL PATHOGENS	→	CARDIO-RENAL	→	DPARP
Intra-Division Dates	3/90 - 5/92		5/92 - 10/97		10/97 - 6/06		6/06 - 4/11		4/11 - present
IND #s and Date Filed	BB-IND #3462 3/90	→	IND # changed to 39,250	→	39,250	→	39,250	→	39,250
Drug Development Milestones and Agreements with FDA (Event and Time)	<p>First randomized, placebo-controlled study (AMP-502) completed July 1991;</p> <p>Second randomized, placebo-controlled study (AMP-502T) completed September 1991</p>	→	<p>End of Phase II meeting 12 November 1996;</p> <p>Treatment protocol (AMP-511) initiated March 1997;</p>	→	<p>Third randomized, placebo-controlled study (AMP-516) completed February 2004;</p>	→	<p>NDA #22-151 submitted 10/10/07;</p> <p>NDA #22-151 resubmitted 4/25/08;</p> <p>NDA #22-151 accepted 7/7/08;</p> <p>NDA #22-151 CRL received 11/25/09;</p>	→	<p>Complete Response to CRL accepted for Review 8/10/12;</p> <p>Advisory Committee Meeting 12/20/12</p>
Phase of Clinical Research	Phase I and Phase II Studies	→	Phase I and Phase II Studies, and Treatment Protocol	→	Phase II and Phase III Studies, and Treatment Protocol	→	Phase II and Phase III Studies, and Treatment Protocol	→	Treatment Protocol

AMP-502 Study (Foundation for AMP-516): Sequelae

- FDA Advisory Committee (Antiviral): A comprehensive (0.5 day) review of final AMP-502 results resulted in **approval of study design of AMP-516**
- Distinguished Program Data Safety Monitoring Board (DSMB):
 - Members: Brown University Vice Chair, Medicine; University of California (San Francisco), Senior Biostatistician; former Physician-in-Chief, Sloan-Kettering Memorial Institute; Johns Hopkins, former Associate Dean in Medicine; Rector, Trinity Church (Wall Street) (One full day review)
 - **Opinion: Affirmed favorable efficacy/safety profile of Ampligen in correspondence with FDA Commissioner**

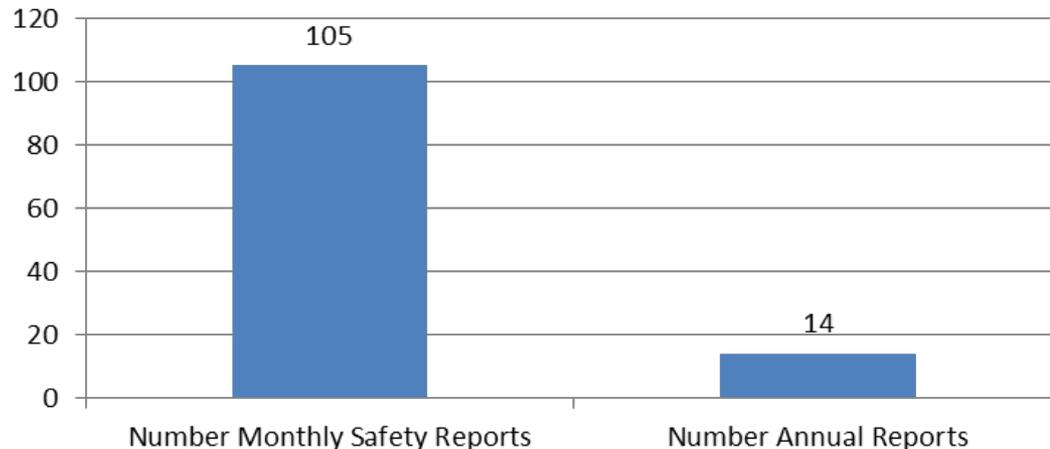
Exercise Tolerance Testing (ETT) as a Measure of Efficacy in CFS

- Symptoms of the disorder are reproduced by the physiologic stressor ETT
- Efficacy conclusions rely on ETT, and are also supported by multiple patient outcomes
- All ETT determinations were performed under stringent criteria using an **independent** team of trained exercise physiologists **blinded** to randomization code

Treatment IND (AMP-511)

- Thereafter:
 - **Treatment protocol with Cost Recovery granted for Ampligen (May 1, 1997) by Dr. Janet Woodcock, Director, CDER.** Treatment protocol program thereafter has operated continuously in USA
 - The resultant treatment IND (AMP-511) has submitted **119 Safety Reports** to FDA in support of a comprehensive safety profile. Numerous requests for **Export Authorization** were granted by FDA. **Pediatric treatment also granted**

**AMP-511 Safety Reports to FDA
Submitted to IND 39,250**



Ampligen Exposure

- Ampligen has been generally well-tolerated in clinical trials enrolling:
 - >1200 patients (all indications)
 - >800 patients with CFS, and
 - >94,000 doses administered: **no drug related deaths, no treatment emergent clinical or lab evidence of new autoimmune signals**
 - >200 patients have received Ampligen for 1 - 2 years*
- * **Exceeds exposure intended for NON-LIFE threatening conditions: *FDA Guidance for Industry: Premarketing Risk Assessment, March, 2005***

Re: FDA Comments on Pre-Clinical Studies Predicting Clinical Toxicities of Ampligen

Hemispherx:

- A wide variance in Ampligen toxicities is observed in test animals with an approximately **100x greater acute toxicity**, for example, between rabbits and non-human primates
- These differences are observed in 3-6 month studies at administered **doses** significantly **exceeding those used clinically** in humans
- The observed fundamental differences in toxicities are due to a) major alteration in TLR-3 gene structure/location/modulation in rodents versus humans and b) **significantly greater half-life of Ampligen in lower animals vs. humans**
- **Thus, the relative toxicity/safety profile of Ampligen is generally not predicted from pre-clinical rodent studies**

Sponsor's Response to FDA Specific Safety Concerns Directed to Advisory Committee

1. Liver Function Abnormalities

- In Ampligen pivotal studies, no evidence of clinical toxicity per Hy's Law (***FDA Guidance on Drug Induced Liver Injury, July 2009***)*

2. Autoimmunity Abnormalities

- **No new cases**, less than predicted by comparative analysis with Cervarix[®] (TLR-4, a product given to healthy adolescents, FDA approved, 2007)
- **No new cases in ≥ 600 patient exposure years with Ampligen**

3. Infusion Reactions

- Managed under REMS program by physician education, low dose useful at treatment inception

* One confounding case, details presented by Dr. Strayer dosing continued without LFT recurrence. Sponsor will conclusively demonstrate REMS program works properly for adverse reactions which are infusion-related

**David R. Strayer, M.D.
Medical Director,
Hemispherx Biopharma, Inc.**

Outline of Clinical Presentation

- 1) Safety**
- 2) Efficacy**

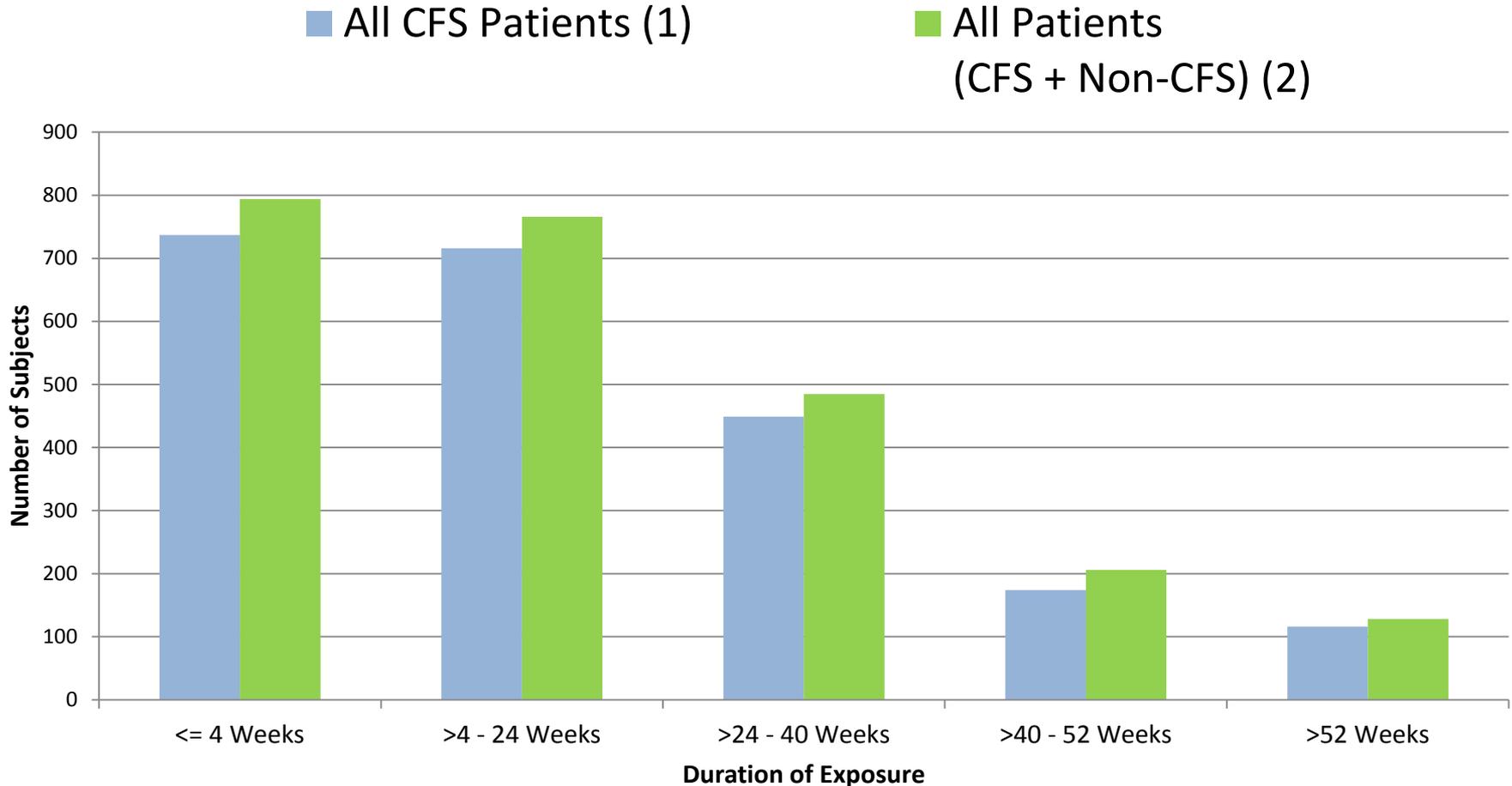
Agenda - Safety

- Overview
- Drug Exposure
- AEs/SAEs
- Clarification of Issue Noted by FDA
- Discuss evidence for no increase risk of:
 - Cancer
 - Autoimmunity
 - Depression and Suicide Ideation/Attempt
 - QT Interval Prolongation
- Safety Conclusion

Overview

- Extensive exposure to drug, including two placebo-controlled studies
- Generally safe and well-tolerated
- Slow intravenous infusion over 30 to 60 minutes
- This CFS specific treatment allows for reduction in symptom directed therapy (e.g. current standard of care)
- Favorable safety profile overall and specifically for QT Interval, Autoimmunity, Hospitalization for Depression/Suicide Attempt, and Cancer

Number of Subjects Who Received Ampligen by the Duration of Exposure (CFS and Non-CFS patients)



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

2 Studies AMP-502 and 516; AMP-501, 502T, 502E, 504, 509, and 516C/E; AMP-511 at last safety cutoff and Studies 700 (HIV), 700E (HIV), 800 (Hepatitis B), and 900(Burn patients)

Drug Exposure in the Ampligen CFS Program

Category	Controlled Pivotal Studies		Controlled and Uncontrolled Studies	
	Studies 502 and 516		CFS Studies ¹	
	Ampligen	Placebo	Ampligen	Placebo
Number of Patients Treated	162	164	737 [589*]	174
Mean Patient-Years on Study Drug	0.63	0.66	0.68	0.65
Total Patient-Years on Study Drug	101.6	109.0	498.6	113.7
Mean Number of IV Infusions	64.1	67.4	59.8	67.0
Total Number of IV Infusions	10389	11051	44054	11656

¹ Studies 501, 502, 502T, 502E, 504, 509, 511 (at last safety cut-off), 516, and 516C/E

* Number of unique patients

Incidence of Adverse Events in the Ampligen CFS Program

Parameter Related to Adverse Events	Controlled Pivotal Studies		Controlled and Uncontrolled Studies	
	Studies 502 and 516		CFS Studies ¹	
	Ampligen	Placebo	Ampligen	Placebo
Number of patients treated	162	164	737 [589*]	174
Number of AEs	2827	2488	11448	2652
Incidence of AEs per 100 Patient-Years on Study Drug	2783	2283	2296	2332
Patients With AEs, n (%)	161 (99%)	160 (98%)	685 (93%)	170 (98%)
Discontinuations, n (%) [%*]	28 (17%)	20 (12%)	98 (13%) [17%*]	20 (11%)
Discontinuations Secondary to AEs, n (%) [%*]	5 (3.1%)	5 (3.0%)	22 (3.0%) [3.7%*]	5 (3.0%)

¹ Studies 501, 502, 502T, 502E, 504, 509, 511 (at last safety cut-off), 516, and 516C/E

* Number of unique patients or % based on unique patients

Summary of All Patients with Adverse Events with at Least 5% Difference Between Ampligen and Placebo

Parameter Related to Adverse Events		Controlled Portions of Pivotal Phase 3 Studies	
		Studies 502 and 516	
		Ampligen	Placebo
		(N=162)	(N=164)
Patients with Any Adverse Events		161 (99.4 %)	160 (97.6 %)
Adverse Events	% Difference*		
FLU SYNDROME	13.9	72 (44.4 %)	50 (30.5 %)
HEADACHE	12.8	74 (45.7 %)	54 (32.9 %)
CHILLS	9.4	27 (16.7 %)	12 (7.3 %)
FEVER	8.2	33 (20.4 %)	20 (12.2 %)
VASODILATATION	7.6	27 (16.7 %)	15 (9.1 %)
PAIN	7.3	75 (46.3 %)	64 (39.0 %)
INJECTION SITE REACTION	7.1	50 (30.9 %)	39 (23.8 %)
PRURITUS	7.0	33 (20.4 %)	22 (13.4 %)
DIARRHEA	6.3	36 (22.2 %)	26 (15.9 %)
SYNCOPE	6.2	13 (8.0 %)	3 (1.8 %)
EAR DISORDER	5.7	22 (13.6 %)	13 (7.9 %)
NAUSEA	5.4	67 (41.4 %)	59 (36.0 %)
MIGRAINE	-5.3	16 (9.9 %)	25 (15.2 %)
ALOPECIA	-5.4	6 (3.7 %)	15 (9.1 %)

¹ Studies 501, 502, 502T, 502E, 504, 509, 511 (at last safety cut-off), 516, and 516C/E

*Ampligen % - placebo %

Local Infusion Site Reactions Occur in About 1% of Infusions Overall

Parameter Related to Infusion Site Reactions	Controlled Pivotal Studies		Controlled and Uncontrolled Studies	
	Studies 502 and 516		CFS Studies ¹	
	Ampligen	Placebo	Ampligen	Placebo
Number patients treated	162	164	737	174
Number of patients with infusion site reaction (%)	50 (31%)	39 (24%)	172 (23%)	39 (22.%)
Total number of infusions	10389	11051	44054	11656
Total number of local infusion site reactions (%) ²	131 (1.3%)	83 (0.8%)	434 (1.0%)	83 (0.7%)
Number of severe infusion site reactions (%)	6 (4.6%)	1 (1.2%)	9 (2.1%)	1 (1.2%)

¹ Studies 501, 502, 502T, 502E, 504, 509, 511 (at last safety cut-off), 516, and 516C/E

² As a percent of total number of infusions or % based on unique patients

Note: In controlled studies the majority of the local infusion site reactions were mild or moderate (93% Ampligen vs. 98.8% placebo) 15 Ampligen infusions out of 44,054 resulted in a severe local reaction

Systemic Infusion Reactions - Flu-Like Symptoms

Parameter Related to Flu-like Symptoms	Controlled Pivotal Studies		Controlled and Uncontrolled Studies	
	Studies 502 and 516		CFS Studies ¹	
	Ampligen	Placebo	Ampligen	Placebo
Number patients treated	162	164	737	174
Number of patients with flu-like symptoms (%)	139 (86%)	120 (73%)	572 (78%)	128 (74%)
Total number of flu-like symptoms	546	414	2858	440

¹ Studies 501, 502, 502T, 502E, 504, 509, 511 (at last safety cut-off), 516, and 516C/E

Note: In controlled studies the majority of the flu-like symptoms were mild or moderate (89% Ampligen vs. 92.5% placebo). The percentage of flu-like symptoms that were severe was 11% (Ampligen) vs. 7.5% (placebo)

Incidence of Serious Adverse Events (SAEs) in the Ampligen CFS Program

Category	Controlled Pivotal Studies		Controlled and Uncontrolled Studies	
	Studies 502 and 516		CFS Studies ¹	
	Ampligen	Placebo	Ampligen	Placebo
Number of Patients Treated	162	164	737 [589*]	174
Number of SAEs	22	22	83	24
Incidence of SAEs per 100 Patient-Years on Study Drug	21.7	20.2	16.6	21.1
Patients With SAEs including Deaths, n (%) [%*]	17 (10.5%)	13 (7.9%)	60 (8.1%) [10.2%*]	15 (8.6%)
Discontinuation Secondary to SAE or Death, n (%) [%*]	1 (0.62%)	1 (0.61%)	8 (1.09%) [1.36%*]	1 (0.57%)
Discontinuations Secondary to SAE/Death per 100 Patient-Years	0.98	0.92	1.60	0.88

¹ Studies 501, 502, 502T, 502E, 504, 509, 511 (at last safety cut-off), 516, and 516C/E

* Number of unique patients or % based on unique patients

AMP 502 & AMP 516: No Significant Difference in the Relationship of SAEs to Study Drug as Determined by Blinded Investigators

Relationship to Study Drug	Number of Serious Adverse Events	
	Ampligen	Placebo
Not Related	16	16
Remote	4	3
Possible	2	2
Probable	0	1
Definite	0	0
Total	22	22

Note: Determination of the number and relationship of SAEs to study drug was done as they occurred during the studies while under double-blinded conditions

Subjects Who Experienced at Least One SAE that was Possibly, Probably, or Definitely Related to Study Drug¹

Study Treatment	Center/ Subject Number	Sex, M/F Age ² , yr	Adverse Event (investigator text)	Reason Why the Event was Considered Serious	Time from Start of Treatment to Becoming Serious, Days	Duration of Event	Action Taken with Respect to Study Drug	Causality as Assessed by the Investigator
AMP-516 Ampligen	53/011	F 28	Suicide attempt (Suicide attempt)	Life-threatening	121	Resolved in 3 Days	Continued	Possible
AMP-502 Ampligen	13/072	F 39	Abdominal pain (Abdominal pain)	Hospitalization	36	Resolved in 5 Days	Continued	Possible
AMP-516 Placebo	37/019	F 42	Chest pain (Difficulty breathing, chest tightness)	Hospitalization	117	Not resolved	Discontinued	Probable
AMP-516 Placebo	52/037	F 35	Convulsion (Seizures)	Hospitalization	251	Not resolved	Discontinued	Possible
AMP-502 Placebo	23/031	F 31	Headache (Accelerated headache syndrome)	Hospitalization	155	Resolved in 9 Days	Continued	Possible

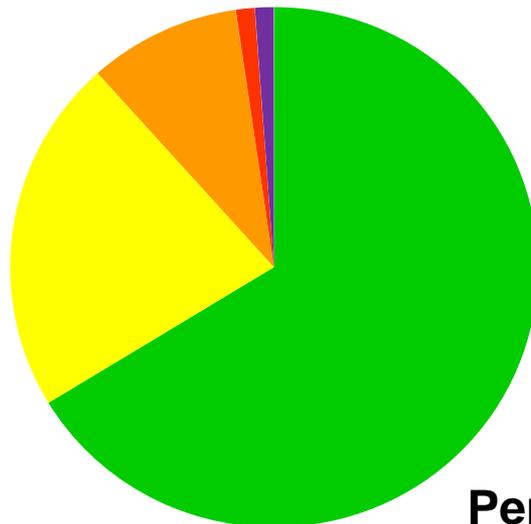
¹ Controlled studies AMP-502 and AMP-516

² Age at enrollment

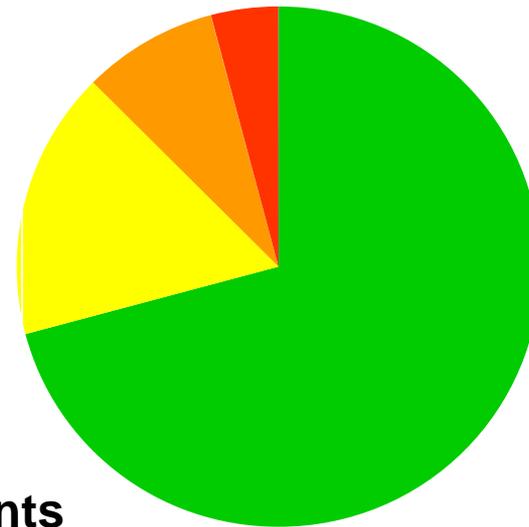
All SAEs in the Ampligen CFS Program – No Significant Difference¹ Between Ampligen and Placebo Groups in Relationship of SAEs to Study Drug

All CFS Studies²

Ampligen Group



Placebo Group



Percent of Patients with SAEs

7.7% ← → 8.6%

¹ Fisher's Exact Test, p=0.74

² Studies 501, 502, 502T, 502E, 504, 509, 511 (at last safety cut-off), 516, and 516C/E

Differences Between Sponsor's SOP for Determining SAE Numbers and FDA's Approach

- The Adverse Event CRF page included a “Hospitalization Required” column which was used to capture Emergency Room Visits, as well as, Inpatient Hospitalizations
- Therefore, a Yes in this section did not necessarily translate into a SAE. Because of this, Hemispherx separately tracked all SAEs which occurred
- The FDA counted Emergency Room Visits which were not in-patient hospitalizations as SAEs
- These ER visits were also not considered SAEs by the Investigators

Differences Related to Counting AEs Associated with SAEs

- Any AE that was associated with an SAE that required hospitalization was also marked “Hospitalization Required” to indicate its association
- For example, a patient with a seizure requiring hospitalization also had the following AEs – tonic spasms, twitching and tingling, all co-tracked with the seizure
- Sponsor counted one SAE = seizure
- The FDA also counted the three AEs for a total of four SAEs

Example of FDA Counting SAEs

- A patient was admitted to the hospital because of a suicide attempt
- Sponsor reported this as an SAE
- After discharge and **three** days after the above hospitalization the patient “admitted” [meaning “acknowledged”] that she had been feeling anxious....., but was not admitted to the hospital a second time
- FDA counted this as a second SAE **three** days after the first
- Hemispherx counts this as one event

Incidence of Deaths in the Ampligen CFS Program: None were Related to Study Drug

Parameter Related to Deaths	Controlled Pivotal Studies		Controlled and Uncontrolled Studies	
	Studies 502 and 516		CFS Studies ¹	
	Ampligen	Placebo	Ampligen	Placebo
Number of Patients Treated	162	164	737 [589*]	174
Deaths, n (%) [%*]	0	0	3² (0.41%) [0.51%*]	0
Incidence of Death Per 100 Patient-Years on Study Drug	0	0	0.60	0

¹ Studies 501, 502, 502T, 502E, 504, 509, 511 (at last safety cut-off), 516, and 516C/E

² These 3 deaths were not related to study drug

Two deaths occurred in AMP-516C/E (38LC 22-RHW with pneumonia and hemoptysis secondary to coagulopathy from warfarin (Prothrombin Time (PT) was 7.7 times normal (INR=7.7) indicating a high risk for bleeding), died of respiratory failure, and 54MS 11-GAC with road rage, was cornered by police and committed suicide). 34DB 024-M-R with a history of depression committed suicide after completing study AMP-509

* Unique number of patients or % based on unique patients

Neoplasia and Cancer: No Increased Incidence of Cancer with Ampligen

Parameter Related to Neoplasia or Cancer	Controlled Pivotal Studies		Controlled and Uncontrolled Studies	
	Studies 502 and 516		CFS Studies ¹	
	Ampligen	Placebo	Ampligen	Placebo
Number patients treated	162	164	737 [589*]	174
Number of patients with neoplasia including benign lipoma (%) [%*]	1 (0.6%)	2 (1.2%)	9 (1.2%) [1.5%*]	2 (1.1%)
Total number of patients with cancer (%) [%*]	1² (0.62%)	1 (0.61%)	2 (0.27%) [0.34%*]	1 (0.57%)

¹ Studies 501, 502, 502T, 502E, 504, 509, 511 (at last safety cut-off), 516, and 516C/E

² **This patient had a pre-existing malignancy before starting Ampligen**

* Number of unique patients or % based on unique patients

Note: The overall higher incidence of neoplasia (9) relative to cancer (2) in the Ampligen cohort is related to the occurrence of benign lipomas (3), benign polyps (2), benign fibroid (1), and benign thyroid nodule (1)

Autoimmunity: No New Onset of Autoimmune Disease with Ampligen

Parameter Related to Autoimmunity	Controlled Pivotal Studies		Controlled and Uncontrolled Studies	
	Studies 502 and 516		CFS Studies ¹	
	Ampligen	Placebo	Ampligen	Placebo
Number patients treated	162	164	737 [589*]	174
Number of patients with pre-existing autoimmune disease (%) [%*]	0	0	2 (0.27%) [0.34%*]	0
Number of patients with new onset of autoimmune disease	0	0	0	0
Number of patients with flares that continued to receive Ampligen [%*]	0	0	2 (0.27%) [0.34%*]	0

¹ Studies 501, 502, 502T, 502E, 504, 509, 511 (at last safety cut-off), 516, and 516C/E

* Number of unique patients or % based on unique patients

No Evidence for Induction of Autoantibodies with Ampligen: Assessment of Anti-dsDNA and Rheumatoid Factor in 64 Randomly Selected Patients in Controlled Study AMP-516 at Week 32

Number of patients	Ampligen		Placebo	
	35		29	
Autoantibody (AB) Test	Anti-dsDNA	Rheumatoid Factor (RF)	Anti-dsDNA	Rheumatoid Factor (RF)
Number of patients with Baseline negative ABs who developed positive ABs at Week 32, n (%)	0 / 35 0%	0 / 35 0%	0 / 29 0%	1 / 27* 3.7%

* Two placebo patients had a positive Rheumatoid Factor (RF) at Baseline

Only induction seen was RF in one placebo patient

No Evidence for an Increase of Treatment Emergent Depression or Suicide Attempt/Ideation with Ampligen

	Controlled Pivotal Studies		Controlled and Uncontrolled Studies	
	Studies 502 and 516		CFS Studies ¹	
	Ampligen	Placebo	Ampligen	Placebo
Number patients treated	162	164	737	174
Number of patients with AEs of depression, hospitalization for depression, or suicide attempt/ideation (%)	19 (11.7%)	21 (12.8%)	62 (8.4%)	22 (12.6%)
Total number of occurrences of the above AEs	25	42	87	43
Incidence of the above AEs per 100 patient years on study drug	0.25	0.39	0.17	0.38

¹ Studies 501, 502, 502T, 502E, 504, 509, 511 (at last safety cut-off), 516, and 516C/E

Increases in Liver Function Tests (SGOT and SGPT >3 ULN) Rarely Resulted in Discontinuation from Study

Parameter Related to SGPT (ALT)	Controlled Portions of Pivotal Studies		Controlled and Uncontrolled Studies	
	Studies 502 and 516		CFS studies ¹	
	Ampligen	Placebo	Ampligen	Placebo
Number patients treated	162	164	737 [589%*]	174
SGPT (ALT) or SGOT (AST) >3X ULN, n (%) [%*]	12 (7.4%)	3 (1.8%)	30 (4.0%) [5.1%*]	3 (1.7%)
SGPT (ALT) or SGOT (AST) >5X ULN, n (%) [%*]	5 (3.1%)	2 (1.2%)	14 (1.9%) [2.4%*]	2 (1.1%)
SGPT or SGOT >3X ULN and total bilirubin > 2X ULN, n (%) Hy' s Law	1 (0.6%)	0	0	0
Discontinuations secondary to abnormal liver function tests, n (%)² [%*]	0 (0%)	0 (0%)	1 (0.13%) [0.17%*]	0 (0%)
Completed Study n (%) [%*]	10 (83%)	3 (100%)	25 (83%)	3 (100%)

¹ Studies 501, 502, 502T, 502E, 504, 509, 511 (at last safety cut-off), 516, and 516C/E

² Percent of total patients

* Number of unique patients or % based on unique patients

Potential Hy's Law Case was Rechallenged with Ampligen and Completed Study

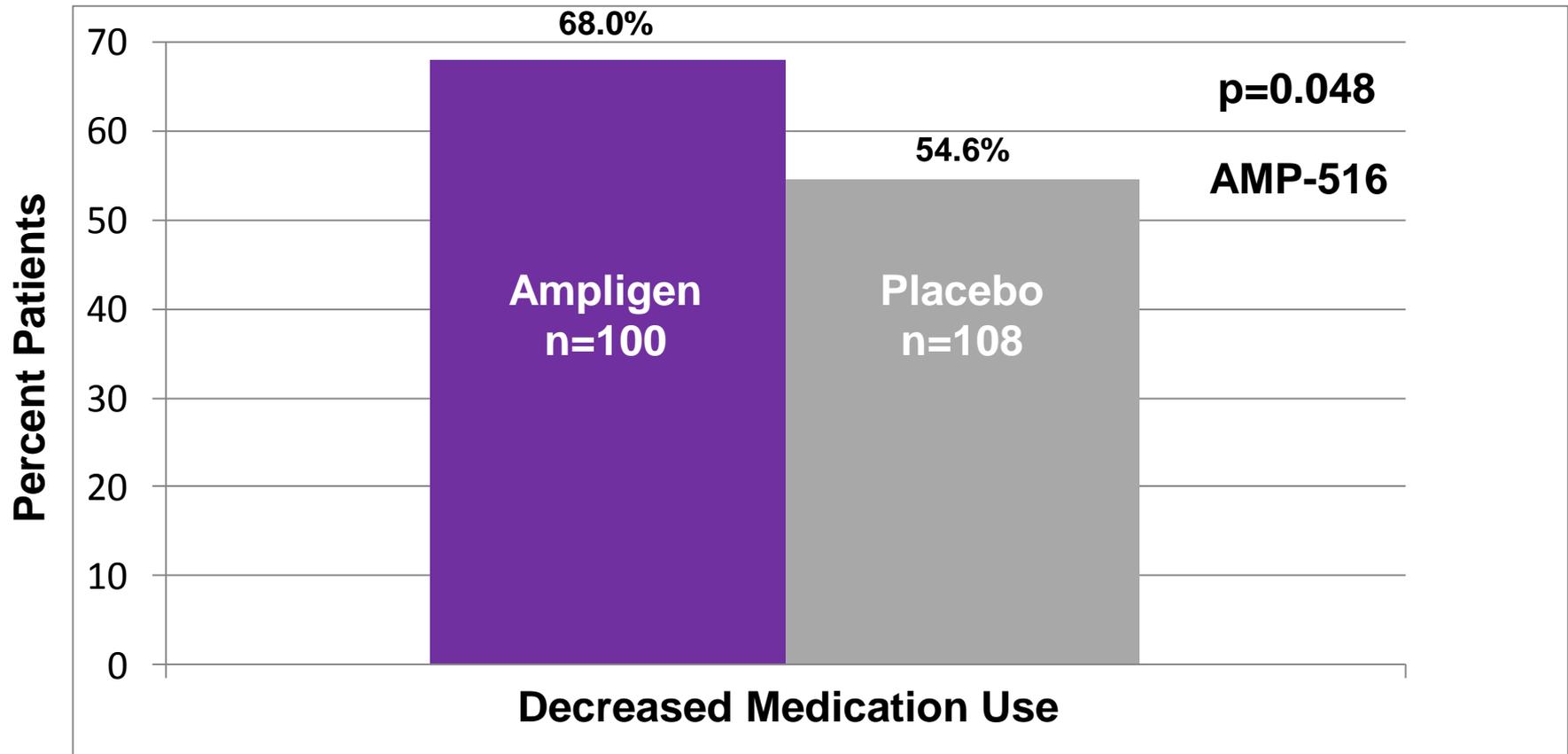
- Elevated ALP – cholestasis - a factor
- History of alcohol consumption - a factor
- LFT elevation was transient
- Rechallenge with Ampligen resulted in patient completing AMP-516 at dose of 200 mg (KPS ↑ 30; ETT ↑ over 80%)
- Completed AMP-516E (24 weeks at 200 mg dose)
- Entered AMP-511 and received 66 weeks of Ampligen therapy at 200 mg dose level without an increase in SGOT/SGPT
- The increases in SGOT/SGPT seen with Ampligen are transient and manageable with dose reductions

Hy's Law and Liver Toxicity

- **Definition:** “Hy’s Law”, or potential for a drug to cause serious liver injury, turns on three factors:
 1. High incidence of 3x or greater increase in SGPT (ALT) or SGOT (AST)
 2. Need a SGPT (ALT) “much greater than 3x”, TBL >2x ULN without cholestasis (without increased ALP)
 3. No other reason found (viral hepatitis, pre-existing disease of other suspect drugs)

See *Guidance for Industry, Drug Induced Liver Injury: Pre-marketing Clinical Evaluations*, July, 2009

Greater Percentage of Ampligen Patients Decrease Use of Concomitant Medications Used in an Attempt to Palliate Symptoms of CFS Compared to Placebo (ITT Population)



¹ The change in use of concomitant medications was calculated for each subject by subtracting the number of days each concomitant medication was taken during the last 4 weeks that the subject was in the study from the number of days each concomitant medication was taken during the first 4 weeks of the study

² p-value is from a chi-square test

Many Concomitant Medications Utilized by CFS Patients have a Known Association for Prolonging the QT Interval

ADDERALL	EPINEPHRINE	PROPULSID
ADIPEX	FASTIN	PROVENTIL INHALER
ALBUTEROL	IMIPRAMINE	PROZAC
ALUPENT INHALER	IMITREX	PSEUDOEPHEDRINE
AMANTADINE	LEVAQUIN	RISPERDAL
AMITRIPTYLINE	LITHOBID	RITALIN
ARALEN	MERIDIA	SEPTRA
AZITHROMYCIN	METHADONE	SEREVENT
BACTRIM	METHYLPHENIDATE	SEROQUEL
BIAXIN	MIDODRINE	SERTRALINE
CELEXA	NEO-SYNEPHRINE 1%	SINEQUAN
CHLOROHYDRATE	NIZORAL	SPORANOX
CIPRO	NORTRIPTYLINE	TECQUIN
DETROL	OXYTOCIN	THIORIDAZINE
DEXEDRINE	PAMELOR	THORAZINE
DIFLUCAN	PAXIL	ZANAFLEX
DROPERIDOL	PHENTERMINE	ZITHROMAX
EFFEXOR	PITOCIN/OXYTOCIN	ZOFRAN
ELAVIL	PROAMITINE	ZOLOFT
		ZOMIG

AMP-516: Evaluation of QT Interval Using the 5 Categorical Classifications of QTc Values Based on E14 Guidance, Number of Ampligen Patients was Never Higher than Placebo (Bazett QTc)

Categorical Classifications E14 Guidance	Treatment	Number of Patients with Abnormal QTc Parameter
>500 msec	Ampligen	0
	Placebo	1
>480 msec	Ampligen	1
	Placebo	1
>450 msec	Ampligen	6
	Placebo	11
>30 msec increase over Baseline	Ampligen	12
	Placebo	19
>60 msec increase over Baseline	Ampligen	1
	Placebo	3

* n=190

AMP-516: Evaluation of QT Interval Using Categorical Classifications of QTc Values Based on E14 Guidance, Number of Ampligen Patients was Never Higher than Placebo (Fridericia QTc)

Categorical Classifications E14 Guidance	Treatment	Number of Patients with Abnormal QTc Parameter
>500 msec	Ampligen	0
	Placebo	0
>480 msec	Ampligen	0
	Placebo	1
>450 msec	Ampligen	1
	Placebo	4
>30 msec increase over Baseline	Ampligen	10
	Placebo	15
>60 msec increase over Baseline	Ampligen	0
	Placebo	3

* n=190

Safety Conclusions

- Extensive long-term exposure including over 100 patients treated for over one year indicates Ampligen treatment for CFS is generally safe and well-tolerated
- Ampligen has a favorable safety profile with **no** evidence for increase in QT Interval, Autoimmunity, Hospitalization for Depression/Suicide Attempt, or Cancer
- Ampligen offers treating physicians and patients a safe CFS directed treatment with a monitorable safety profile

Efficacy

1. Phase III Study (AMP-516)

- Primary endpoint (ETT) was met
- 25% increase in ETT is clinically meaningful
- Greater percentage of Ampligen patients increase by $\geq 25\%$ in ETT than placebo
- Concomitant medication use was decreased

2. Phase II Study (AMP-502)

- Primary endpoint (KPS) was met
- Secondary endpoints supports AMP-516

AMP-516 Phase III Study Design

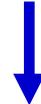
- Randomized, Placebo-controlled
- Double-Blinded, 40 weeks (Stage 1)
- Ampligen Dose = 400 mg
- Twice weekly IV infusions
- Primary Endpoint: Treadmill Exercise Duration
- **The two exercise strata (≤ 9 vs. > 9 minutes) were pre-declared subsets for efficacy analysis and stratified at randomization**
- Full Analysis Set for efficacy consisted of the 208 patients who completed a pre- and post- Baseline exercise tolerance test

AMP-516 Primary Endpoint: Exercise Treadmill Tolerance (ETT) Duration

Prohibited Medication Washout



Baseline Evaluations



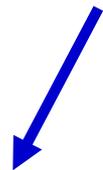
Stratification (Based on Mean of Two Exercise Treadmills):

Treadmill Duration

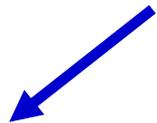
≤ 9 minutes

vs.

> 9 minutes



Randomized



Ampligen



Placebo



Randomized

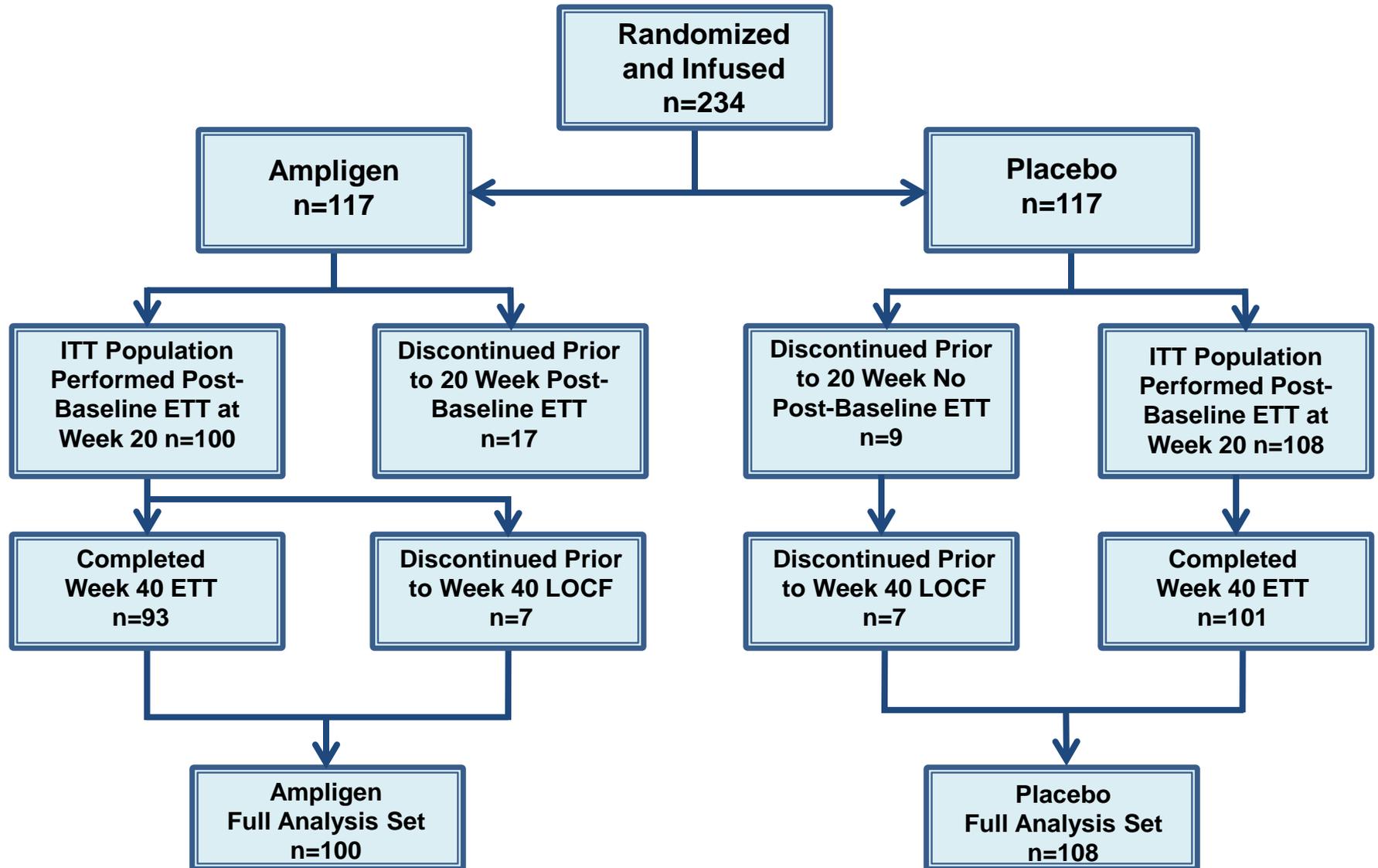


Ampligen



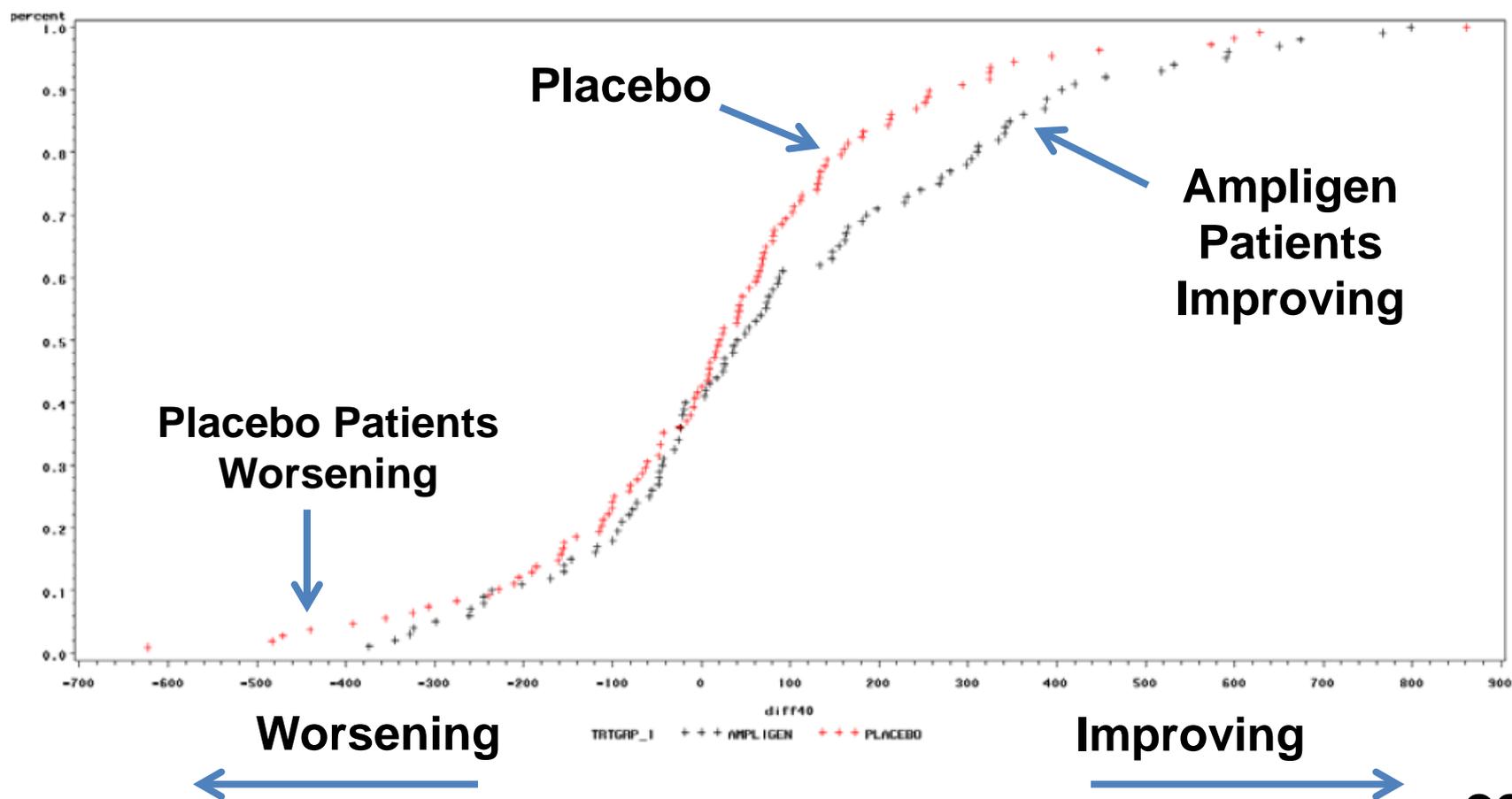
Placebo

AMP-516 Patient Accountability



FDA Distribution Function Shows a Positive Effect of Ampligen

Figure 5: Empirical Distribution Function in the Absolute Change from baseline ETT at 40 weeks (seconds) Study AMP-516 (FDA Briefing Document Page 24)



**Richard P. Chiacchierini, Ph.D.
President and CEO**

R. P. Chiacchierini & Associates

**Former Director, Division of Biometric Sciences,
FDA Center for Devices and Radiological Health**

**Bio-statistical issues in the AMP-516 ETT data
analysis**

- **\log_{10} transformation**
- **Inclusion of covariates used in randomization**

Excerpt from Statistical Section of Last AMP-516 Protocol (Version 4/20/03)

Primary Endpoint:

1. “Treadmill Exercise Tolerance Testing (ETT): Duration”
2. “Efficacy will be established by showing a medically significant increase ($>6.5\%$) in mean exercise duration (baseline compared to week 40) that is statistically significant ($p < 0.05$) using analysis of covariance of \log_{10} transformed data with Baseline ETT duration as covariate. Note: Analysis of past ETT data **suggests** that the \log_{10} transformation will result in compliance of the usual assumptions required for the t-test.”

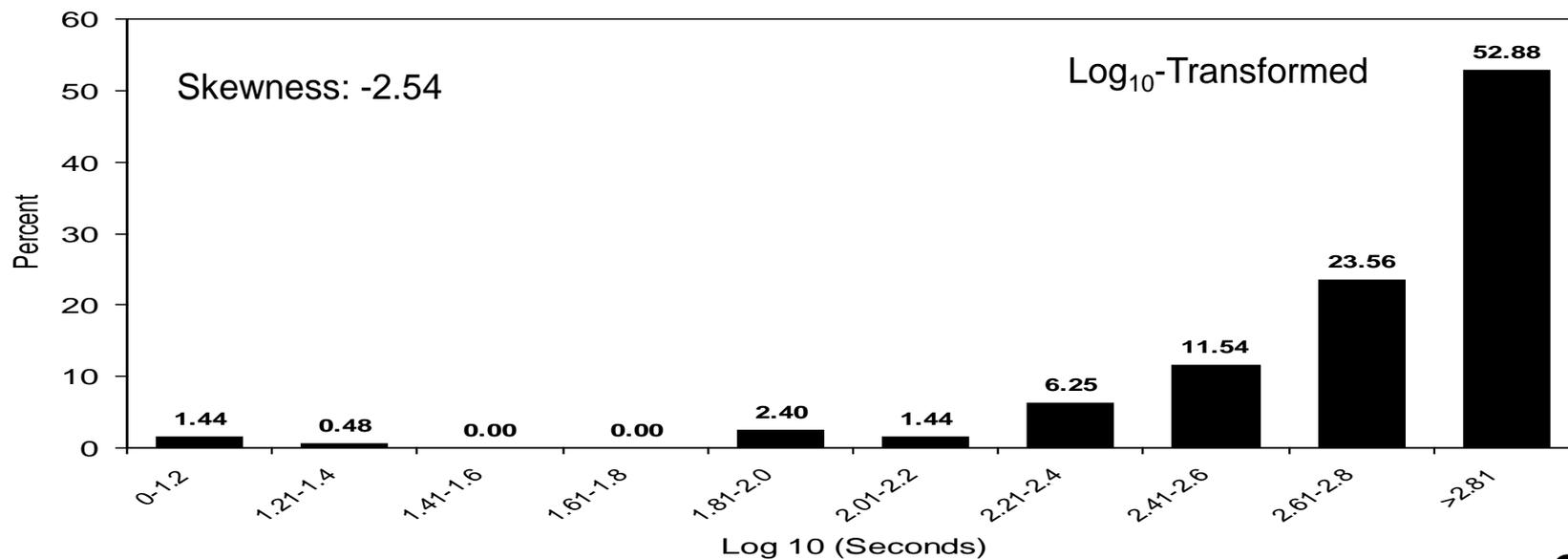
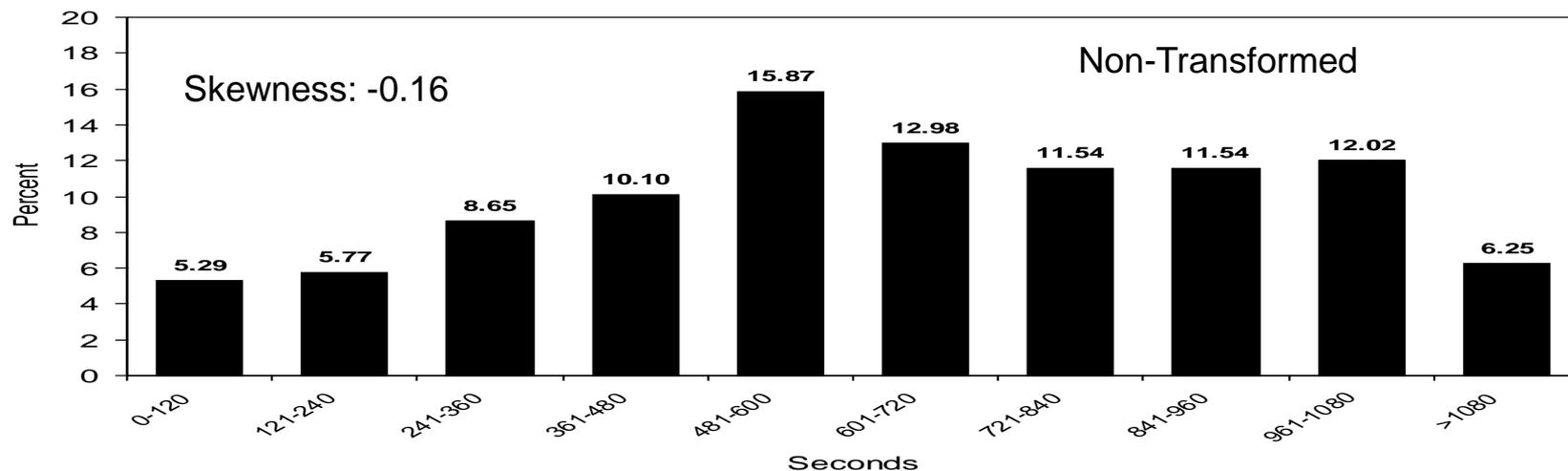
Log₁₀ Transformation or Not

- What are the usual assumptions?
 - Equality of variance between treatment groups
 - Consistency with normality
- Before a statistician modifies the raw data in any way, the need for that modification must be evaluated
 - No transformation should be applied unless it is necessary
 - Transformations can have undesirable effects on data*
 - Transformations make the clinical interpretation challenging
 - FDA's E9 Guidance cautions that if a transformation is used its choice should be “influenced by a preference for scale and facilitate clinical interpretation”

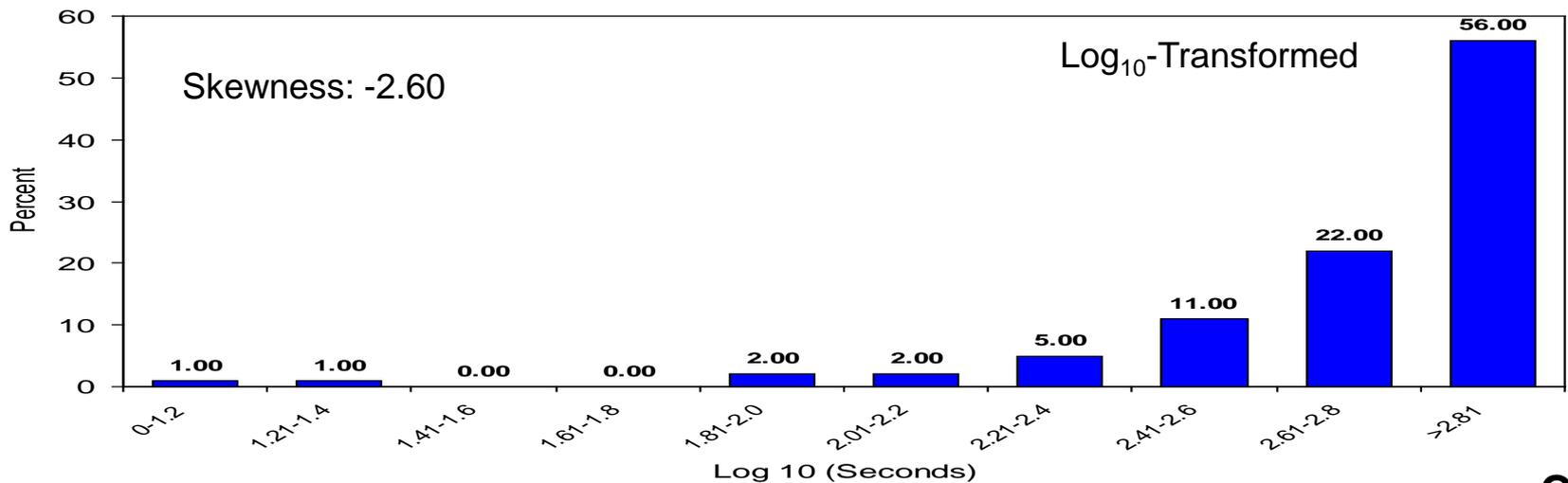
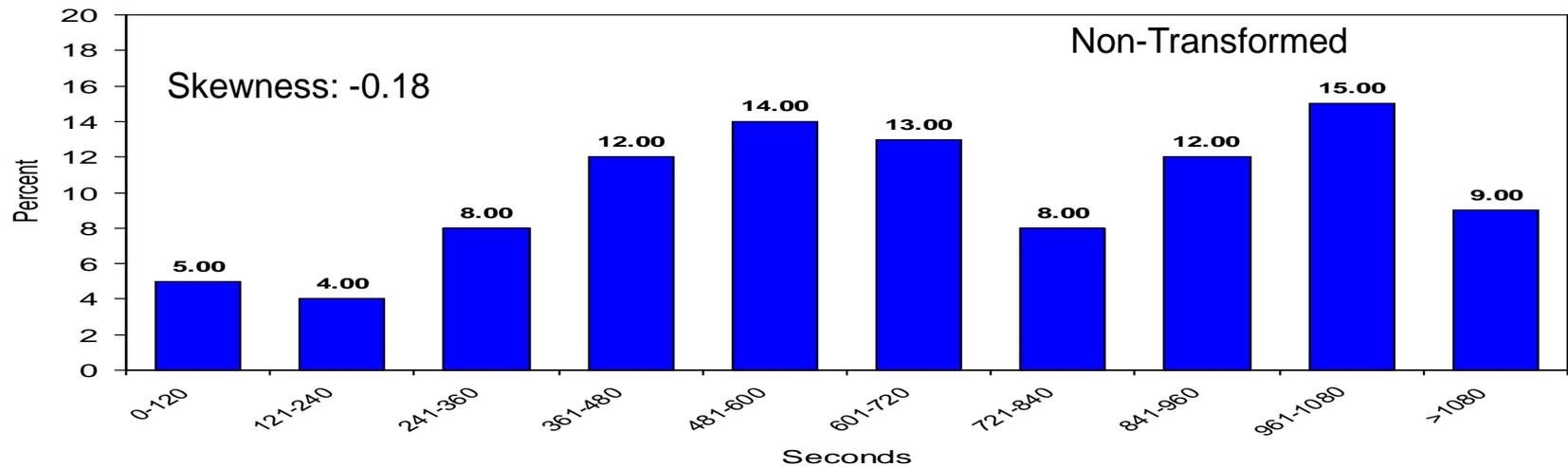
Log₁₀ Transformation or Not (continued)

- Occam's razor as restated by Einstein should be applied to statistical data analysis: Everything should be made as simple as possible, but not simpler
 - Test of the ETT data for the two treatment groups did not indicate that the variances were unequal between the two comparison groups ($p \approx 0.292$, Folded F-Test)
 - Thus, the Log₁₀ transformation is unnecessary to assure equal variance
 - While the transformed data also exhibit equal variance between the groups does the transformation improve the normality of the data?

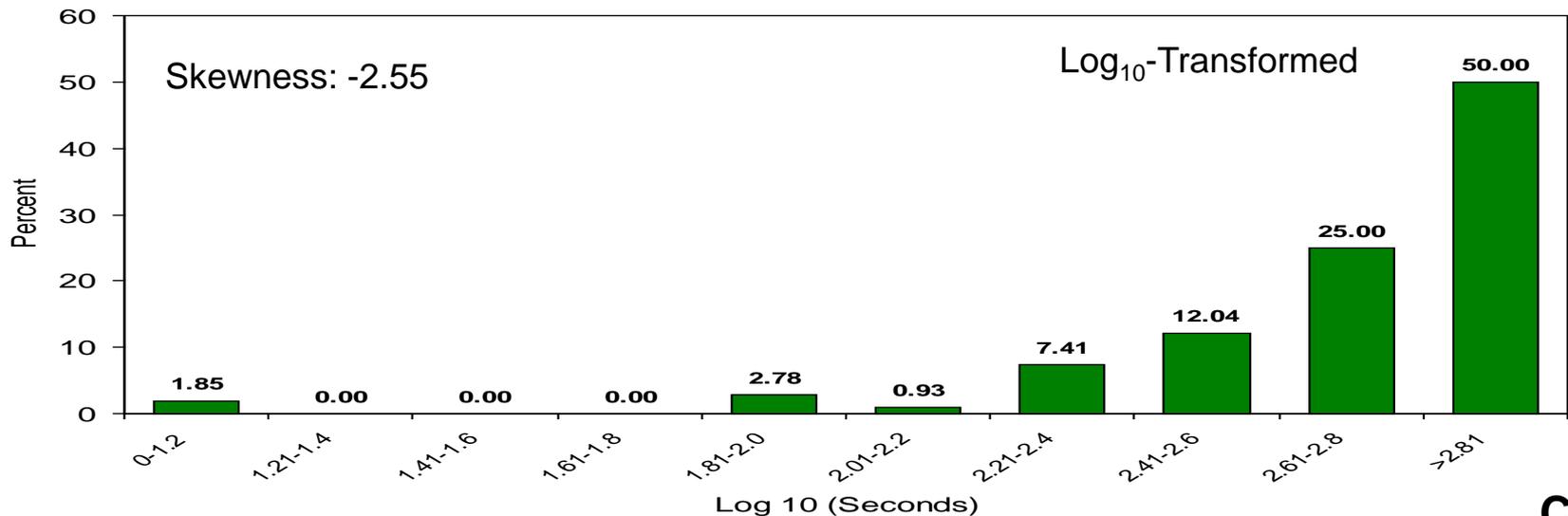
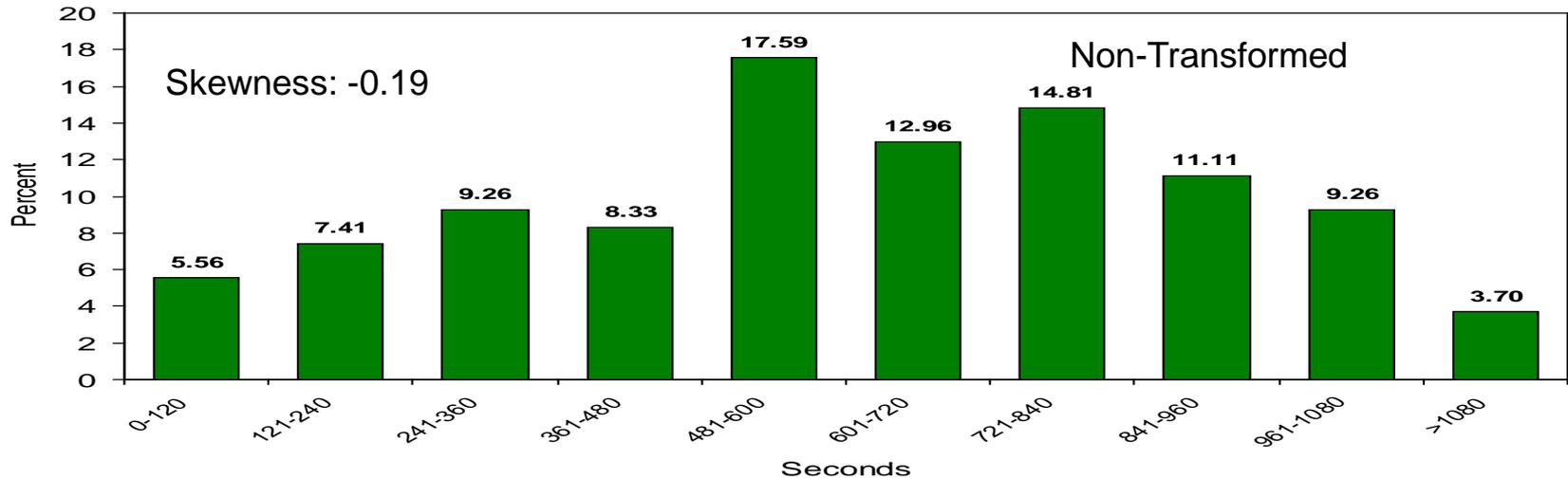
Distribution Comparison of ETT Scores and Log_{10} (ETT Scores) at Week 40: All Patients (AMP-516)



Distribution Comparison of ETT Scores and Log₁₀ (ETT Scores) at Week 40: Ampligen Patients (AMP-516)



Distribution Comparison of ETT Scores and \log_{10} (ETT Scores) at Week 40: Placebo Patients (AMP-516)



Log10 Transformation or Not (continued)

- Clearly the transformed data do not exhibit distributional properties that make the data closer to the normal distribution in fact the opposite is true
- The transformation was not necessary for the equal variance assumption and its application makes the data further from normality than the untransformed data
- Thus for the appropriate analysis, the transformation should not be applied

Inclusion of Covariate in the Model for Variable Used in Randomization

- The randomization scheme was stratified by the patient's baseline ETT value. The stratification was a dichotomization of the ETT range defined as an inclusion criteria for the study. ETT at Baseline was between 0-18 minutes
- It is common practice to include stratification factors that were part of the study design into the primary model for analysis. This is done to increase the precision of the analysis, and to determine if the effect of the active drug is consistent between patients with a baseline ETT time of <9 minutes vs. ≥ 9 minutes, relative to placebo

No Significant Interaction for the Week 40 Landmark Analysis

- The results of the analysis including the ≤ 9 minutes vs. ≥ 9 minutes stratification factor in the model (ANCOVA) revealed there was no significant interaction between treatment assignment and baseline ETT (≤ 9 vs. > 9 minutes) for the Week 40 landmark analysis ($p=0.531$)
- The impact of adding this covariate to the base covariance analysis model will be discussed later in the presentation

Statistical Issues Conclusion

- Pre-specification of transformations should be based on necessity, not by directive
 - It was not needed to satisfy either of the usual assumptions for the analysis method, in fact
 - The transformation made the data decidedly less normal than the untransformed data
- When variables are used in the randomization, Friedman, Furberg and DeMets (1985) state that they should be included as covariates in the analysis of the data
- Pocock et al. (2002) indicate that while it is desirable to pre-specify covariates to be used in the analysis, but “may be unachievable in practice”

Friedman, L., C. Furberg, and D. DeMets. (1985). *Fundamentals of Clinical Trials*. Mosby Year Book, St. Louis

Pocock, S., S. Assmann, L. Enos, and L. Kasten. Subgroup analysis, covariance adjustment, and baseline comparisons in clinical trial reporting: current practice and problems. *Stat. in Med.* 21: 2917-2930, 2002

**David R. Strayer, M.D.
Medical Director,
Hemispherx Biopharma, Inc.**

AMP-516 Primary Efficacy Endpoint: Change from Baseline in Mean ETT Duration at Week 40 is Statistically Significant for the ITT Population

Week	Exercise Duration Mean seconds		Increase from Baseline seconds % increase		Improvement Over Placebo seconds	p-value
	Ampligen	Placebo	Ampligen	Placebo		
Baseline	576.3 n=100	588.1 n=108	-	-	-	-
40	672.0 n=100	616.3 n=108	95.7	28.2	67.5	0.047¹

¹ Analysis of Covariance (Baseline as Covariate) **non-transformed ETT data**

Note: Log₁₀ transformation is in conflict with FDA's E9 Guidance

AMP-516: Baseline ETT Stratification Added to the ANCOVA Model Week 40 Minus Baseline (ITT Population)

Statistic	Ampligen	Placebo
Number of Patients	n=100	n=108
Mean Change (seconds)	95.65	28.25
Paired-difference t-test	<0.001	0.20
ANCOVA Untransformed Data	p=0.047	
ANCOVA with 9 Minutes in model	p=0.033*	

* 1-factor analysis of covariance test – Independent Variables: Treatment, 9 minute-covariates: Baseline ETT Result, ANCOVA for Baseline Comparison

Complete ANCOVA model strengthens the p-value

Increase in Placebo-Adjusted Intra-Group Mean ETT Duration with Ampligen: the ITT and Pre-Declared Subsets Shows Greater Improvement with Ampligen

Efficacy Population (ETT)	Increase from Baseline - seconds		Improvement Over Placebo -seconds	p-value
	Ampligen	Placebo		
ITT Population (Full Analysis Set) (AMP n=100, PLA n=108)	95.7	28.2	67.5	0.047¹ 0.033²
Patients Without a Significant Dose Reduction (AMP n=83, PLA n=98)	109	26	83	0.022¹
Completer Population (AMP n=93, PLA n=101)	108	27	81	0.019¹
Baseline ETT >9 Minutes (AMP n=60, PLA n=66)	+73	-13	86	0.026¹

¹ Analysis of Covariance (Baseline as Covariate) non-transformed ETT data

² 1-factor analysis of covariance test – Independent Variables: Treatment, 9 minute-covariates: Baseline ETT Result, ANCOVA for Baseline Comparison

Clinical Significance is Based on Intra-Group Mean ETT Improvement $\geq 6.5\%$

- Pre-declared as a point estimate in AMP-516 Protocol authorized to proceed in January 1998 (Division of Special Pathogens and Immunologic Drug Products)
- $\geq 6.5\%$ criteria was based on ETT improvement seen with two other drugs approved by the FDA for another chronic condition, chronic heart failure, at the request of FDA
- FDA request of March 24, 1997 (Division of Anti-Viral Drug Products): “Please provide supporting information on the use of this variable to evaluate exercise tolerance in CFS patients **or patients with other chronic diagnoses.**”

Medically Significant Relevance of Mean ETT Change was Modified to Percent Change (Placebo-Adjusted) to Compare to Literature

Chronic Disease Indication	Drug (Placebo-Controlled Clinical Trial)	Group Analyzed	% Improvement Over Placebo [†]
Chronic Fatigue Syndrome	Ampligen (AMP-516)	Intent-to-Treat	11.8
Chronic Heart Failure	Fosinopril ¹	20 mg dosage group	6.7
	Captopril ²	150 mg dosage group	6.2

† Intra-Group Mean ETT Improvement Over Placebo

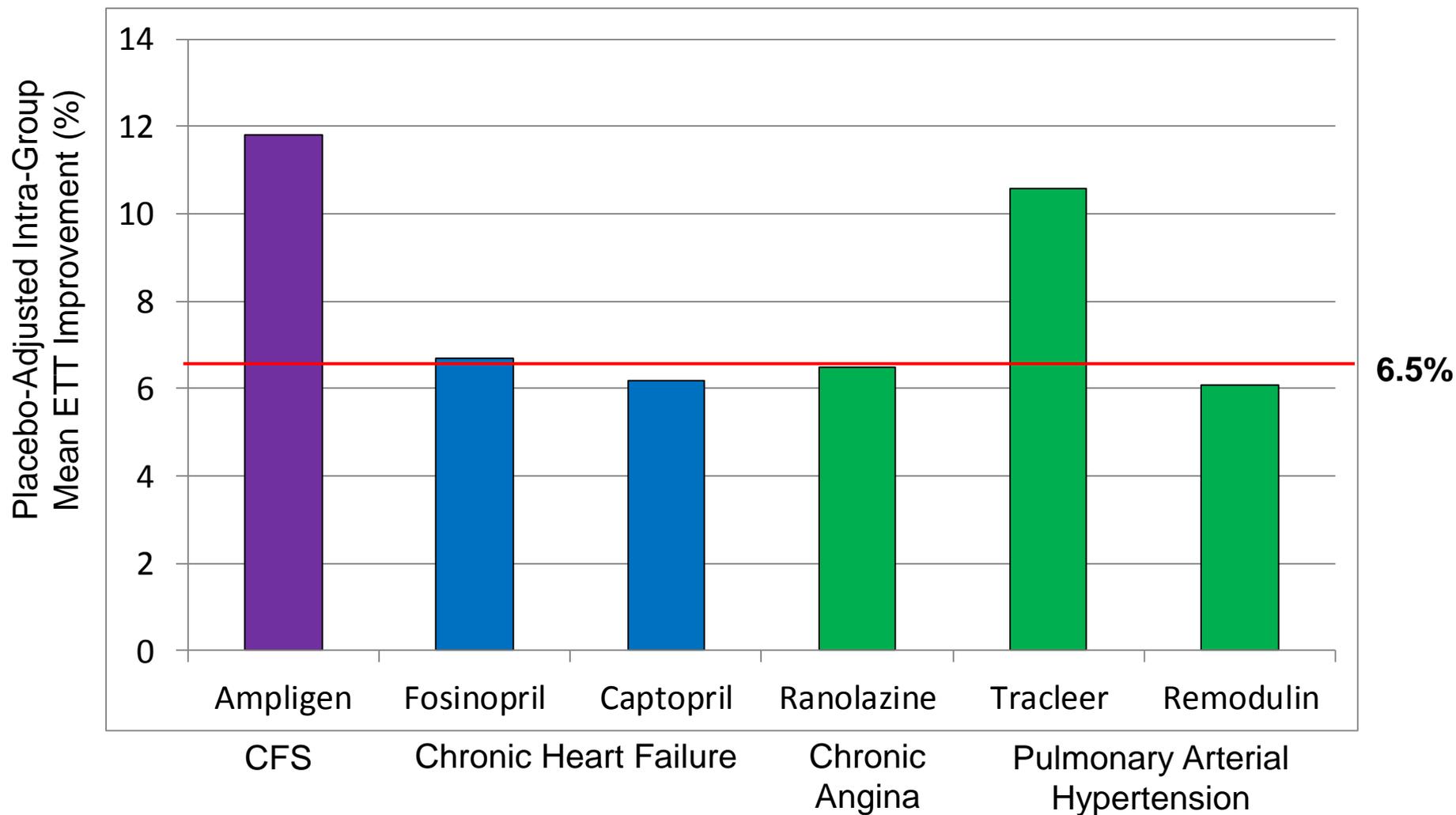
¹ Brown et al. *Am J Cardiol* 1995;75:596-600

² The Captopril-Digoxin Multicenter Research Group *JAMA* 1988;259:539-544

Protocol-Driven Analysis

Point estimate of percent improvement over placebo for Ampligen is 11.8 compared to 6.7 and 6.2 for two FDA approved drugs for non-CFS severe exertional fatigue

The Percent Intra-Group Mean Exercise Improvement for Ampligen for CFS Exceeds Drugs Approved for Non-CFS Severe Exertional Fatigue(Protocol Driven Analysis)



AMP-516 Met Primary Endpoint: Exercise Treadmill Tolerance (ETT)

- Statistical Significance
 - ANCOVA untransformed Data **p=0.047**
 - ANCOVA with Baseline ≤ 9 minutes and > 9 minutes included in the model **p=0.033**
- Medical Relevance
 - Intra-group mean ETT improvement **=11.8%**

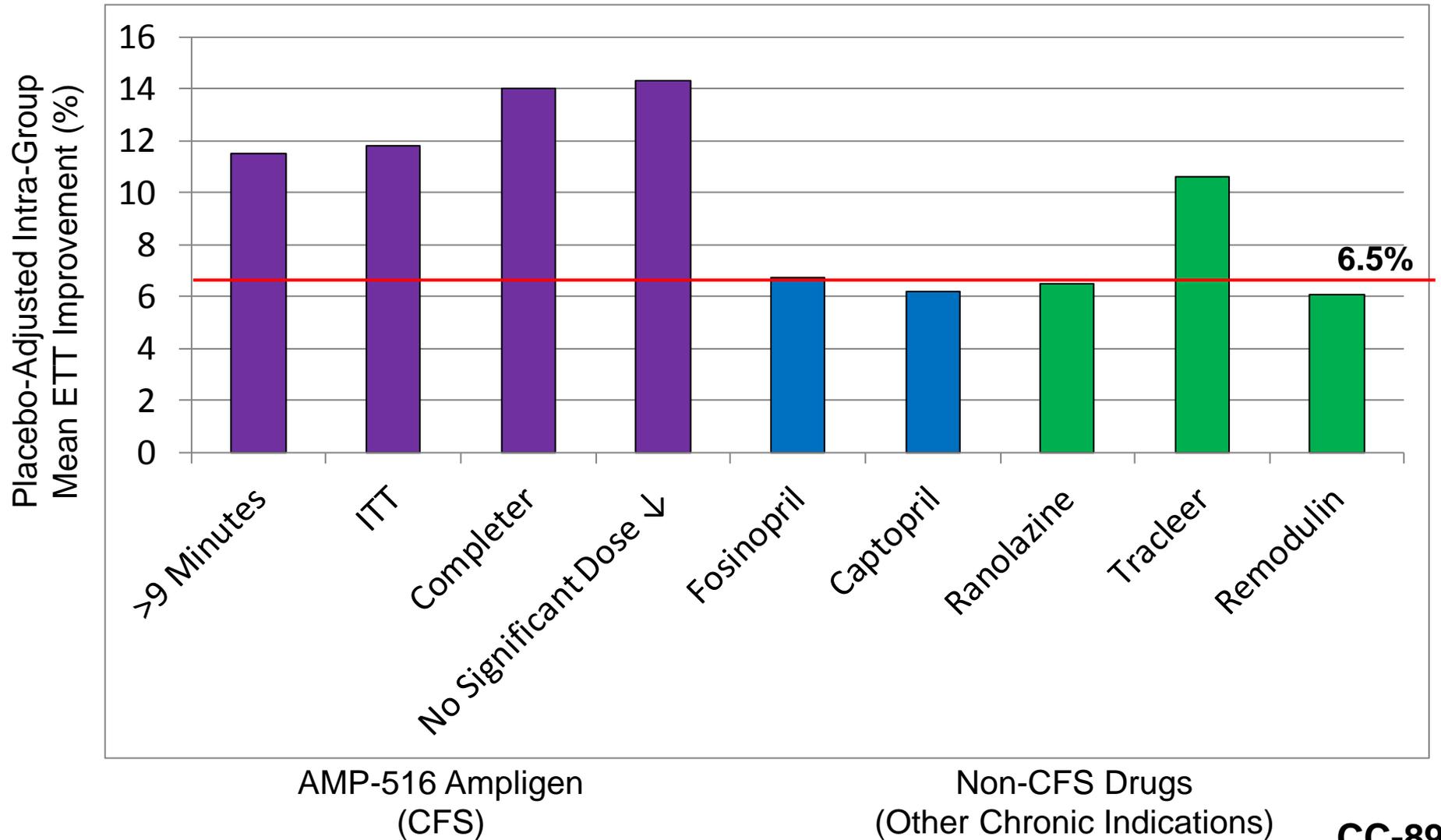
Note: Analysis of medians (used by FDA) leads to uncertainty. Primary endpoint was 6.5% mean change. Use of 6.5% by the FDA is not consistent with the protocol or with Sponsor's intention

Percent Increase in Placebo-Adjusted Intra-Group Mean ETT Duration Shows Greater Improvement with Ampligen for Three Pre-Declared Subsets

Efficacy Population (ETT)	Increase from Baseline – seconds % increase		Improvement Over Placebo –seconds % increase*
	Ampligen	Placebo	
ITT Population (Full Analysis Set) (AMP n=100, PLA n=108)	95.7 16.6%	28.2 4.80%	67.5 11.81%
Patients Without a Significant Dose Reduction (AMP n=83, PLA n=98)	109 18.73%	26 4.47%	83 14.26%
Completer Population (AMP n=93, PLA n=101)	108 18.56%	27 4.60%	81 13.96%
Baseline ETT >9 Minutes (AMP n=60, PLA n=66)	+73 +9.77%	-13 -1.76%	86 11.53%

* Ampligen minus placebo

Comparison of Intra-Group Mean ETT Improvement: Ampligen for CFS Exceeds Drugs Approved for Non-CFS Severe Exertional Fatigue (Protocol Driven Analysis)



Percent Increase in Placebo-Adjusted Intra-Patient Mean ETT Duration Shows Greater Improvement with Ampligen for the ITT and Pre-Declared Subsets

Efficacy Population (ETT)	Increase from Baseline - seconds % increase		Improvement Over Placebo - seconds % increase*	p-value
	Ampligen	Placebo		
ITT Population (Full Analysis Set) (AMP n=100, PLA n=108)	95.7 36.5%	28.2 15.2%	67.5 21.3%	0.047¹ 0.033²
Patients Without a Significant Dose Reduction (AMP n=83, PLA n=98)	109 43.0%	26 15.0%	83 28.0%	0.022¹
Completer Population (AMP n=93, PLA n=101)	108 40.2%	27 15.6%	81 24.6%	0.019¹
Baseline ETT >9 Minutes (AMP n=60, PLA n=66)	+73 12.6%	-13 -1.5%	86 14.2%	0.026¹

¹ Analysis of Covariance (Baseline as Covariate) non-transformed ETT data

* Ampligen minus placebo

² 1-factor analysis of covariance test – Independent Variables: Treatment, 9 minute-covariates: Baseline ETT Result, ANCOVA for Baseline Comparison

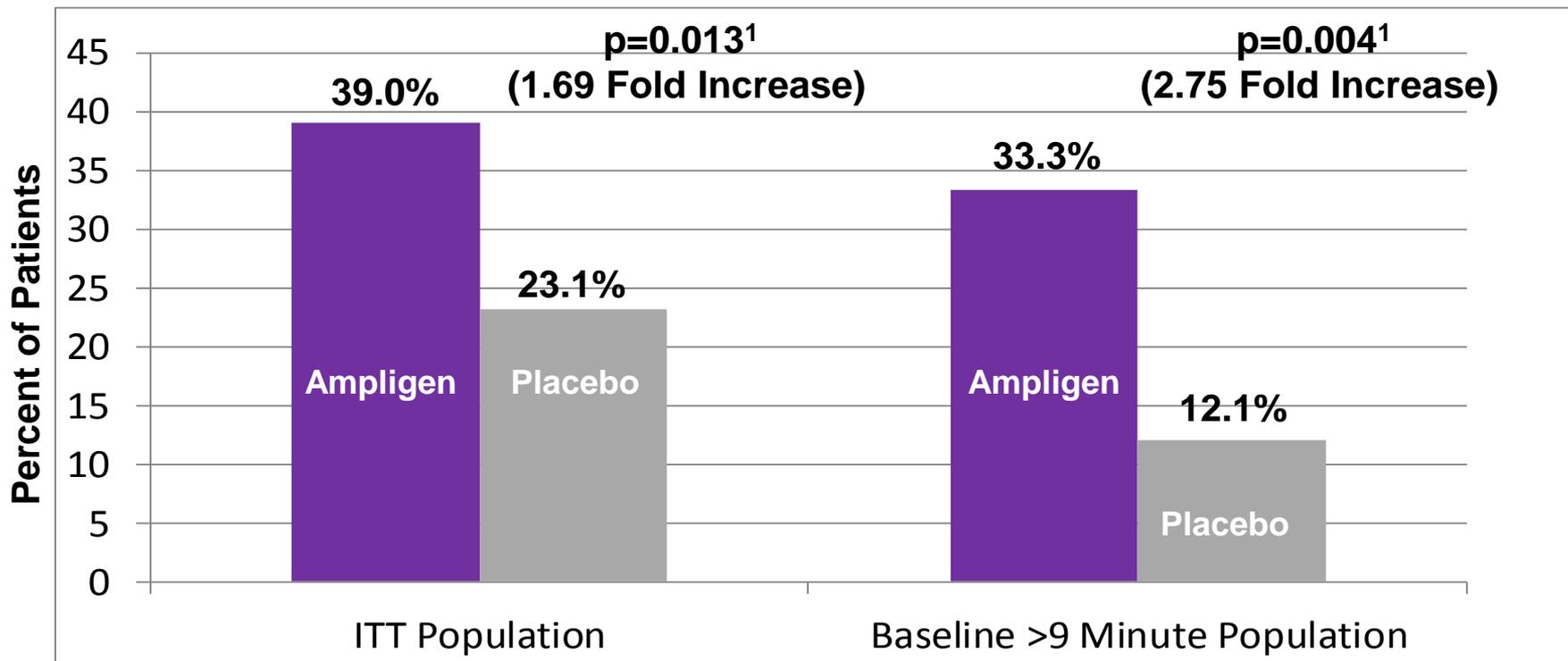
Increase in Exercise Treadmill Duration with Ampligen for the Subset with Baseline ETT Duration >9 minutes is Significant Using Log₁₀ Transformation

Week	Exercise Duration - mean (seconds)		Increase from Baseline - seconds		Improvement Over Placebo -seconds	p-value
	Ampligen	Placebo	Ampligen	Placebo		
Baseline	747 n=60	738 n=66	-	-	-	-
40	820 n=60	725 n=66	+73	-13	86	0.026 ¹ 0.029²

¹ Analysis of Covariance (Baseline as Covariate)

² Analysis of Covariance (Baseline as Covariate) log₁₀ transformed data

AMP-516: Clinical Relevance of at Least a 25% Increase in ETT from Baseline. Greater Improvement with Ampligen Compared to Placebo

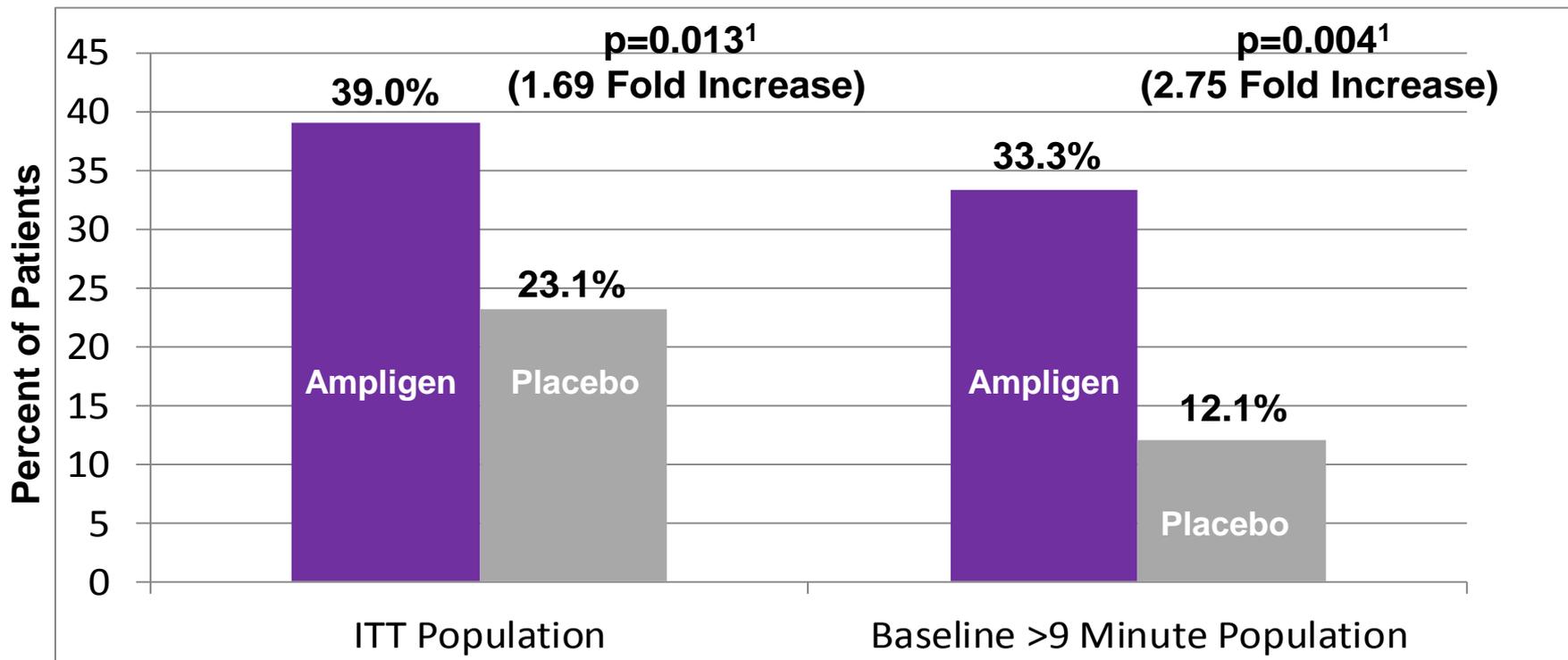


¹ Probability that a difference between treatment groups exists using the Chi-square test

* Originally pre-declared at 20% for KPS, but modified to 25% for ETT based on a request from FDA (Division of Antiviral Drug Products – March 1997) to establish a clinically meaningful percent change that is above intra-patient ETT variability

Post-hoc Analysis based on original protocol and request from FDA

AMP-516: Clinical Relevance of at Least a 25% Increase in ETT from Baseline. Greater Improvement with Ampligen Compared to Placebo



¹ Probability that a difference between treatment groups exists using the Chi-square test

* Originally pre-declared at 20% for KPS, but modified to 25% for ETT based on a request from FDA (Division of Antiviral Drug Products – March 1997) to establish a clinically meaningful percent change that is above intra-patient ETT variability

Post-hoc Analysis based on original protocol and request from FDA

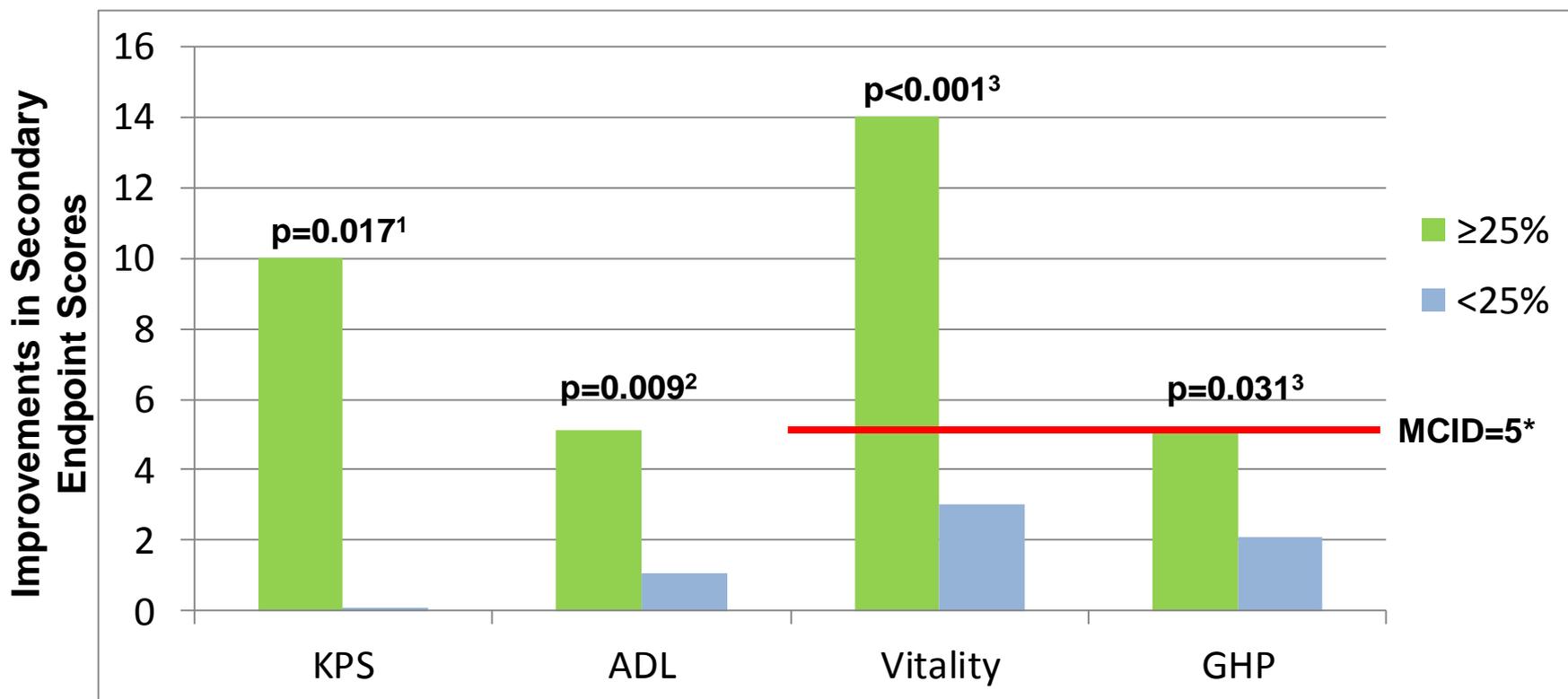
How to Validate that a Change in ETT $\geq 25\%$ is Clinically Significant

The purpose of the next graphic (quality of life) is to evaluate the effect of $\geq 25\%$ ETT improvement on patient reported outcomes (quality of life)

The **composite group** examined was $\geq 25\%$ ETT responders: including both Ampligen treated (the majority of patients) and placebo treated (the minority)

The issue of Ampligen efficacy is deliberately kept separate and is shown in a separate subsequent graphic

Validation of Change in ETT of $\geq 25\%$ as Clinically Significant by Dichotomizing ITT Population Based on $< 25\%$ vs. $\geq 25\%$ Change from Baseline at Week 40 in ETT Duration Shows Corresponding Improvements in Four Secondary Endpoints, KPS, ADL, Vitality and GHP (SF-36)



¹ Median with p-value based on Wilcoxon Two-Sample test (two-sided)

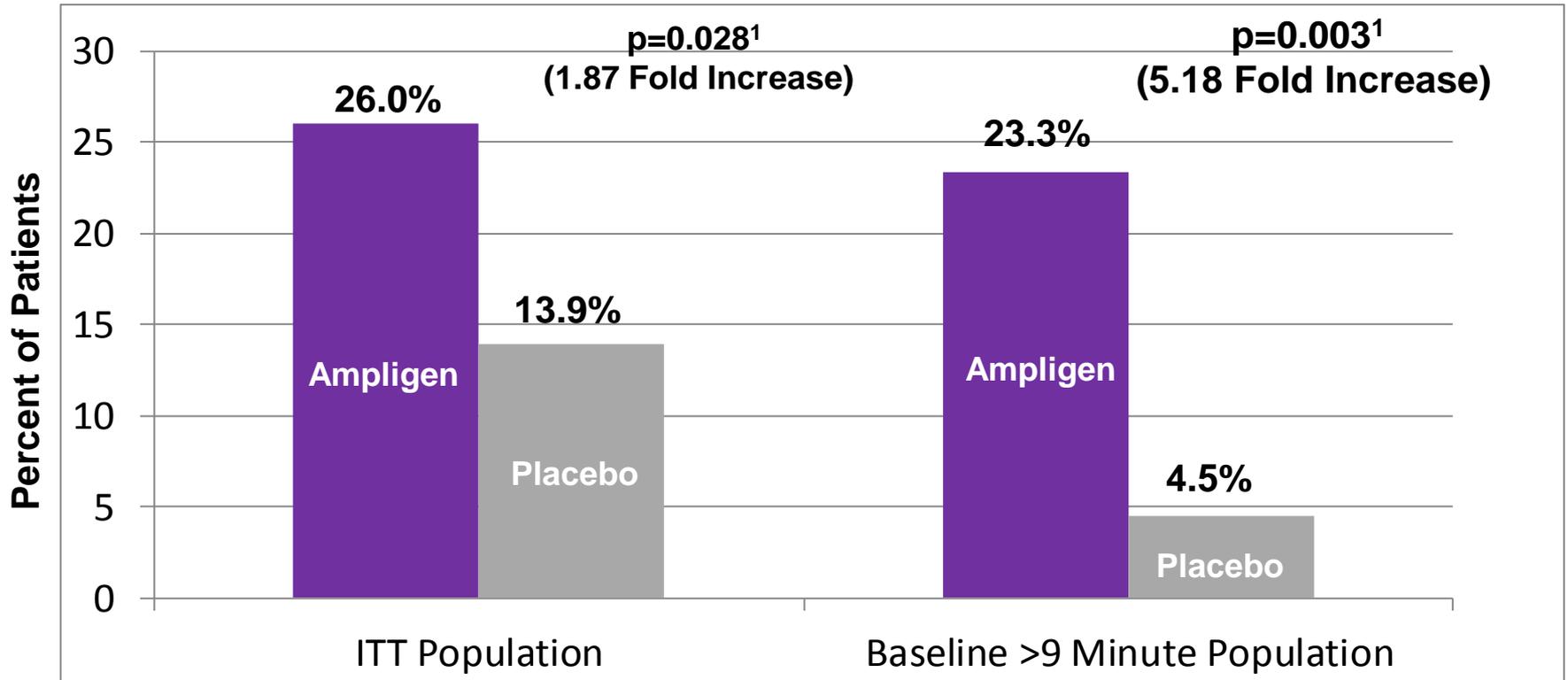
² Mean with p-value based on 1-factor ANOVA model

³ Mean with p-value based on ANCOVA model with Baseline as covariant

*MCID = Minimal Clinically Important Difference

Post-hoc Analysis

AMP-516: Percent of Patients with at Least 50% Increase in ETT from Baseline to Week 40 Also Shows Greater Improvement with Ampligen Compared to Placebo



¹ Probability that a difference between treatment groups exists using the Chi-square test

50% was chosen based on the current medical literature and on the FDA approval of Lyrica for fibromyalgia, a condition with many similarities to CFS.

Frequency Distribution of $\geq 25\%$ Improvement, $< 25\%$ Change and $\geq 25\%$ Worsening in ETT from Baseline at Week 40 Shows 5.9 Fold Greater Net Improvement with Ampligen (ITT Population, Study AMP-516)

Treatment	Worse n (%)	No Change n (%)	Improved n (%)	Net Improvement*	p-value ¹
Ampligen (n=100)	17 (17.0%)	44 (44.0%)	39 (39.0%)	22%	0.044
Placebo (n=108)	21 (19.4%)	62 (57.4%)	25 (23.1%)	3.7%	

¹Probability values derived from the Chi-square test

* Percent improved minus percent worse



**Fold Increase
Over Placebo
= 5.9 Fold**

Frequency Distribution of $\geq 25\%$ Improvement, $< 25\%$ Change and $\geq 25\%$ Worsening in ETT from Baseline at Week 40 Shows 22.9% Net Improvement with Ampligen (Subset of ITT Population with Baseline ETT > 9 Minutes)

Change from Baseline	Treatment	Worse n (%)	No Change n (%)	Improved n (%)	Net Improvement*	p-value
$\geq 25\%$	Ampligen (n=60)	9 (15.0%)	31 (51.7%)	20 (33.3%)	18.3%	0.015 ¹
	Placebo (n=66)	11 (16.7%)	47 (71.2%)	8 (12.1%)	-4.6%	0.014 ²

¹ Probability values derived from the Chi-square test

² 2-tailed Fisher's Exact test

* Percent improved minus percent worse



**Net
Improvement
Over Placebo
= 22.9%**

Frequency Distribution of $\geq 50\%$ Improvement, $< 50\%$ Change and $\geq 50\%$ Worsening in ETT from Baseline to Week 40 Shows a Net Improvement of 27.9% with Ampligen (Subset of ITT Population with Baseline ETT > 9 Minutes)

Change from Baseline	Treatment	Worse n (%)	No Change n (%)	Improved n (%)	Net Improvement*	p-value
$\geq 50\%$	Ampligen (n=60)	0 (0%)	46 (67.7%)	14 (23.3%)	23.3%	p= < 0.001 ¹ p= < 0.001 ²
	Placebo (n=66)	6 (9.1%)	57 (86.4%)	3 (4.5%)	-4.6%	

¹ Chi-square test

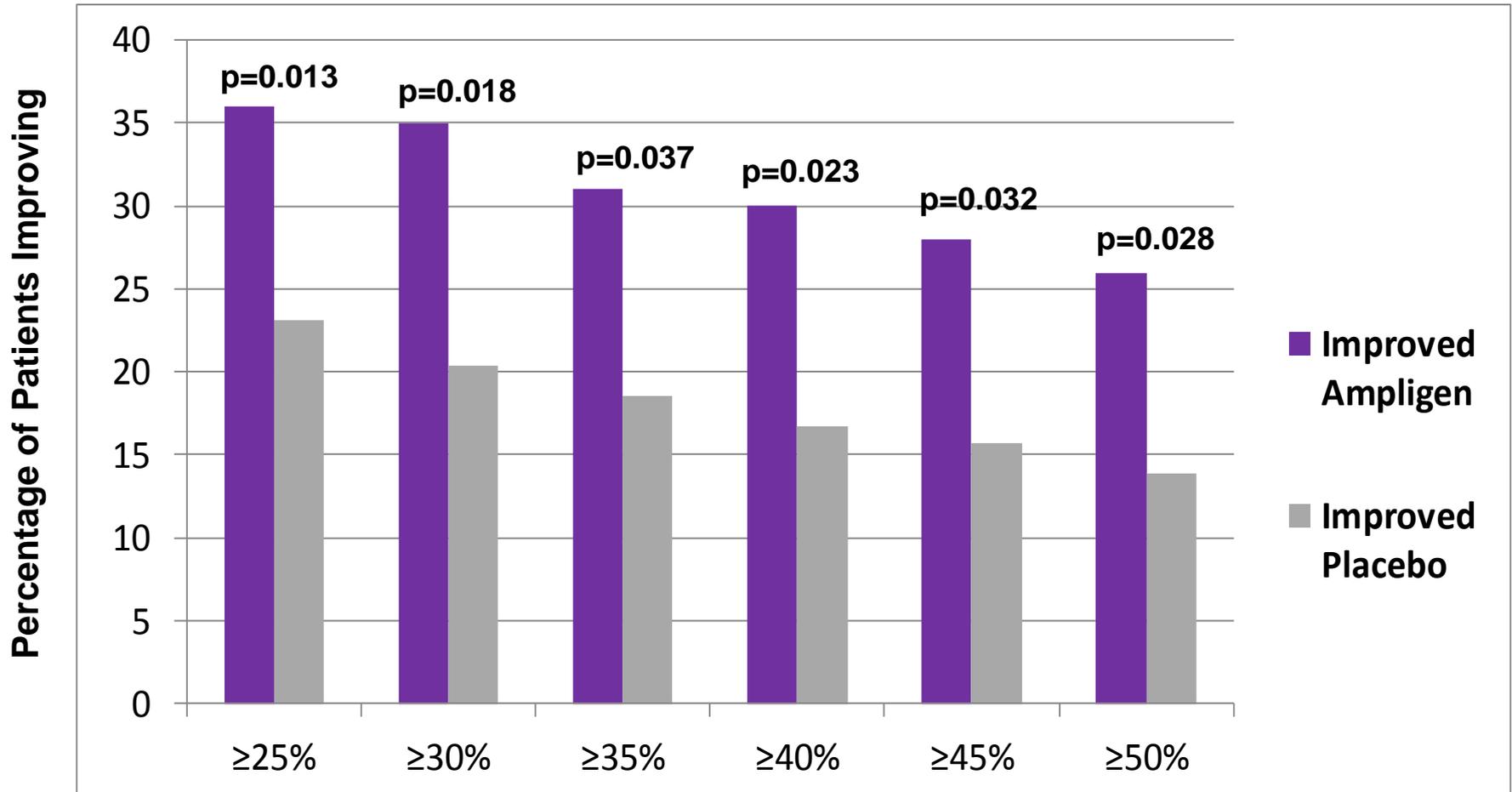
² 2-tailed Fisher's exact test (appropriate if any cell has less than five observations)

* Percent improved minus percent worse



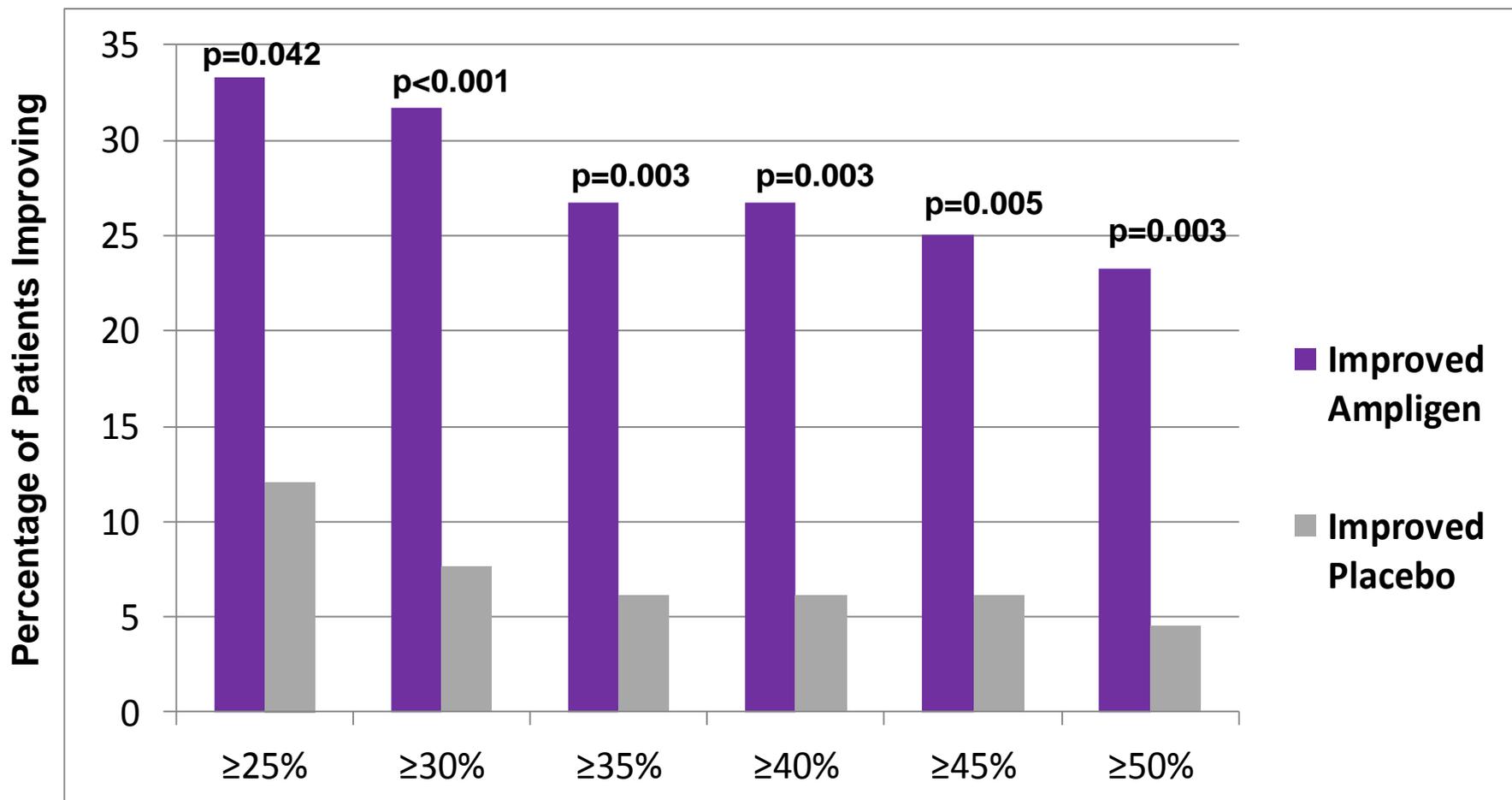
**Net
Improvement
Over Placebo
= 27.9%**

Continuous Analysis of 5% Response Increments Shows a Sustained Ampligen Effect at Each Interval from $\geq 25\%$ to $\geq 50\%$ and Illustrates the Robustness of the Results for the AMP-516 (ITT) (n=208) Week 40



¹ Probability values derived from the Chi-square test

Using the Same Analysis an Even Greater Sustained Ampligen Effect is Seen at Each Interval from $\geq 25\%$ to $\geq 50\%$ and Illustrates the Robustness of the Results at Week 40 for Patients with Baseline ETT >9 Minutes Population (n=126) in AMP-516



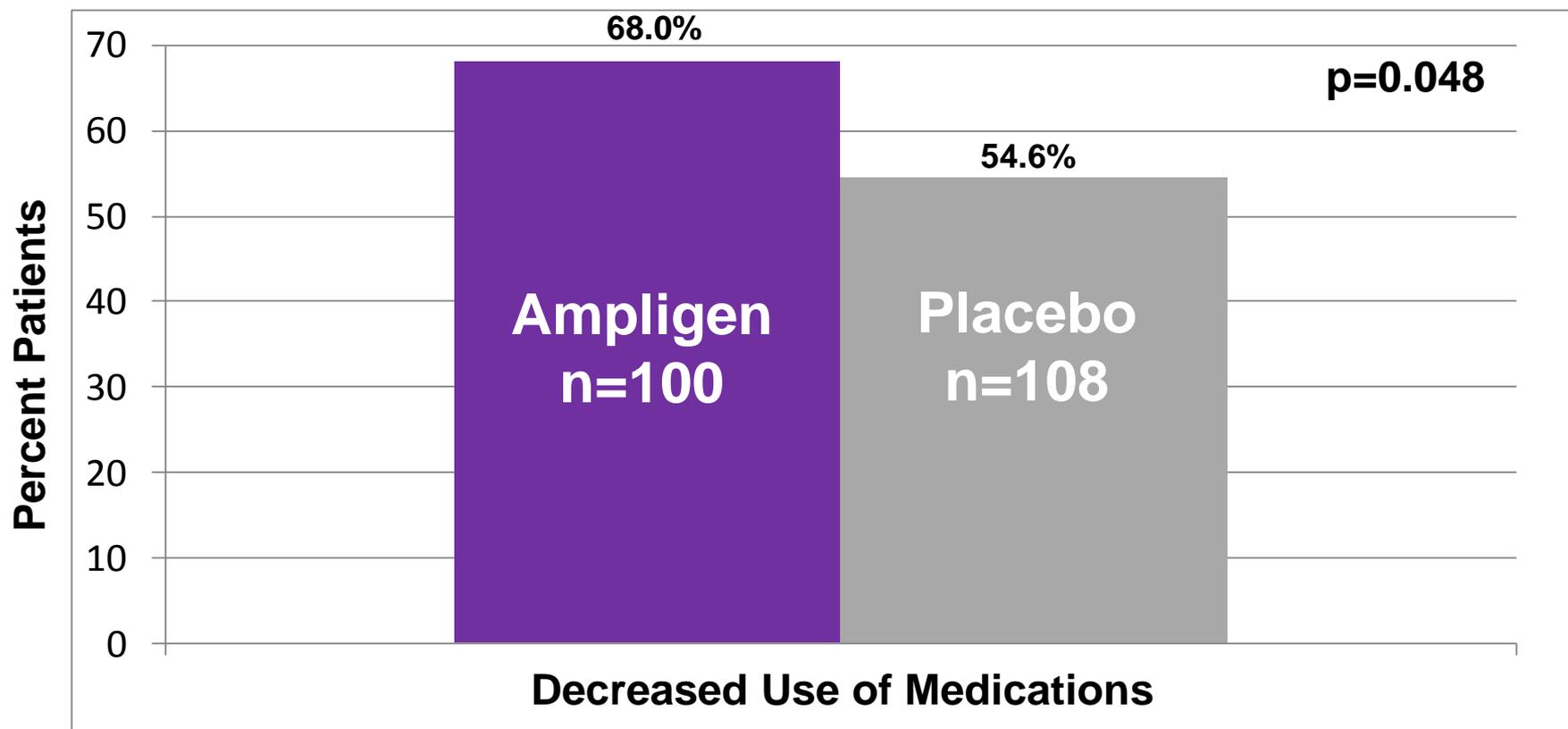
¹ Chi-square test or if any cell has less than five observations, a 2-tailed Fisher's exact test

Categories of Concomitant Medications Used to Palliate Symptoms Associated with Chronic Fatigue Syndrome as Defined by the Centers for Disease Control and Prevention

Symptoms Contained in CDC Case Definition	Main Categories Utilized to Treat Symptoms
Fever	Antipyretics
Sore Throat	Analgesics, Antibiotics
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Arthralgia	Analgesics, NSAIDS, Narcotics, Muscle Relaxants
Neuropsychological Complaints	Thyroid Preparations, CNS Stimulants, Antidepressants, Anticonvulsants, Antianxiety Agents, Anti-panic Agents
Sleep Disturbances	Sedatives, Hypnotics, Analgesics, Narcotics

CFS patients have a lot of symptoms and they utilize many medications in an attempt to palliate these symptoms

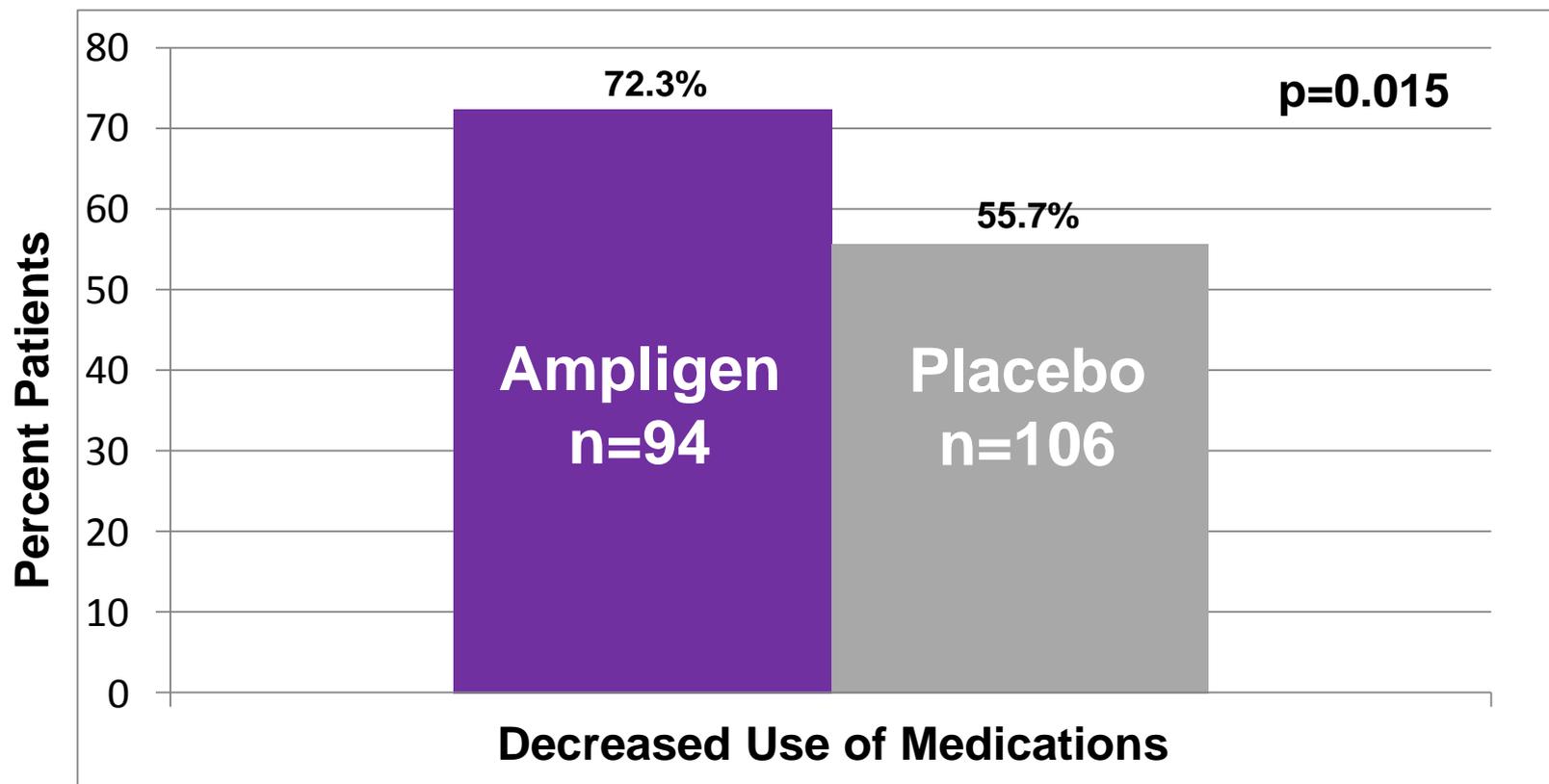
Change from Initial Use of Concomitant Medications to Palliate Symptoms of CFS Shows a Greater Decrease with Ampligen Compared to Placebo (ITT) (AMP-516)



¹ The change in use of concomitant medications was calculated for each subject by subtracting the number of days each concomitant medication was taken during the last 4 weeks that the subject was in the study from the number of days each concomitant medication was taken during the first 4 weeks of the study

² p-value is from a chi-square test

Change from Initial Use of Concomitant Medications Related to CFS at End of Study AMP-516 (ITT Population Who Took at Least One Concomitant Medication) Shows an Even Greater Decrease with Ampligen Compared to Placebo



¹ The change in use of concomitant medication was calculated for each subject by subtracting the number of days each concomitant medication was taken during the last 4 weeks that the subject was in the study from the number of days each concomitant medication was taken during the first 4 weeks of the study ² p-value is from a chi-square test

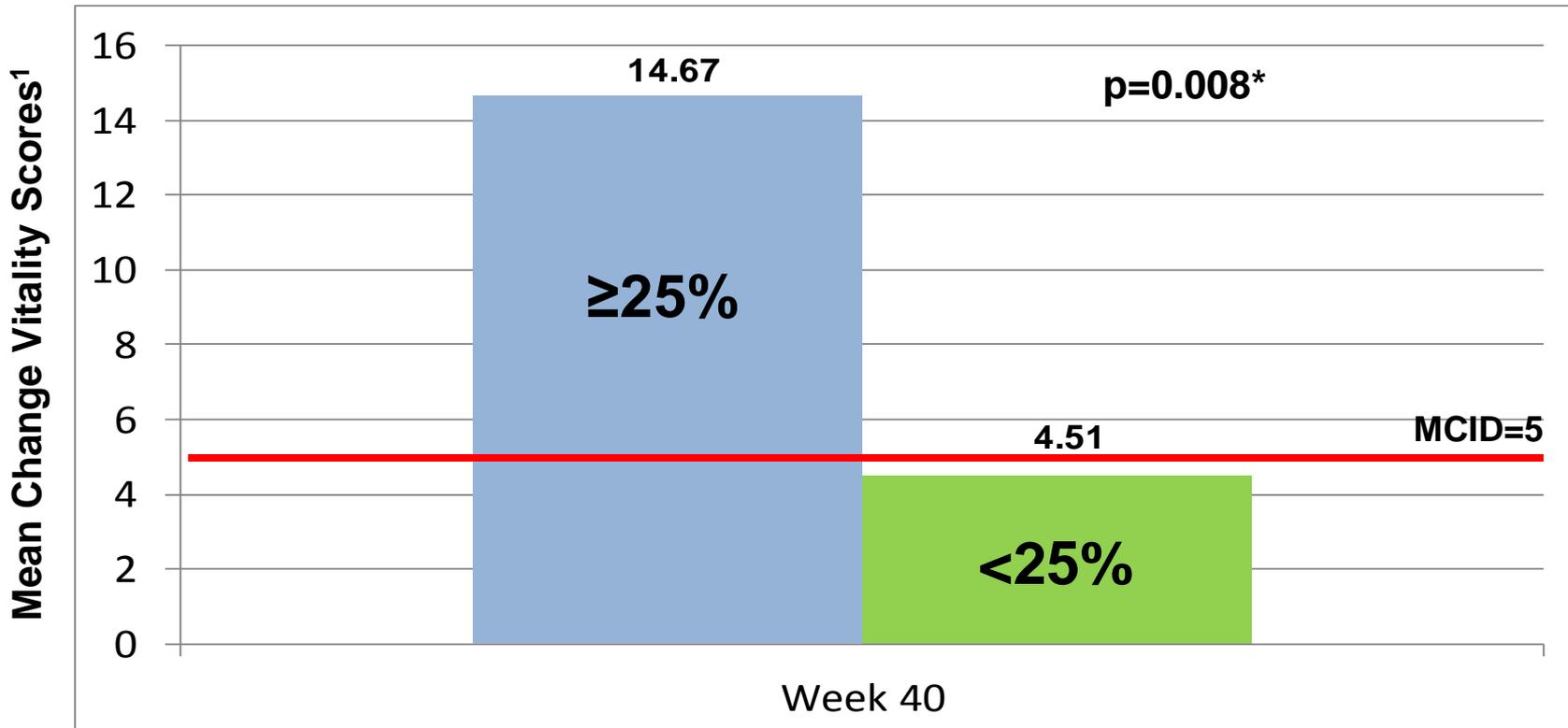
Dichotomizing the Ampligen Treated ITT Population Based on Significant Clinical Improvement ($\geq 25\%$) at Week 40 in ETT Duration Shows There is Corresponding Clinically Significant Improvements in Secondary Endpoints, KPS and Vitality (SF-36) for the $\geq 25\%$ ETT Improving Ampligen Cohort

Secondary Endpoint		Dichotomized by ETT Improvement		p-value
		<25% (n=61)	$\geq 25\%$ (n=39)	
KPS ¹	Baseline	50	50	0.005
	Week 40	50	60	
Vitality ² (SF-36)	Baseline	9.84	9.49	0.008
	Week 40	14.34	24.10	

¹ Median with p-value based on Wilcoxon Two-Sample test (two-sided)

² Mean with p-value based on 1-factor ANOVA model

Vitality Score (SF-36) Increased Over 14 Points from Baseline for Ampligen Patients With a $\geq 25\%$ Improvement in ETT at Week 40 While the Minimum Change to be Clinically Significant is Five (ITT Population)



¹ Mean with p-value based on 1-factor ANOVA model

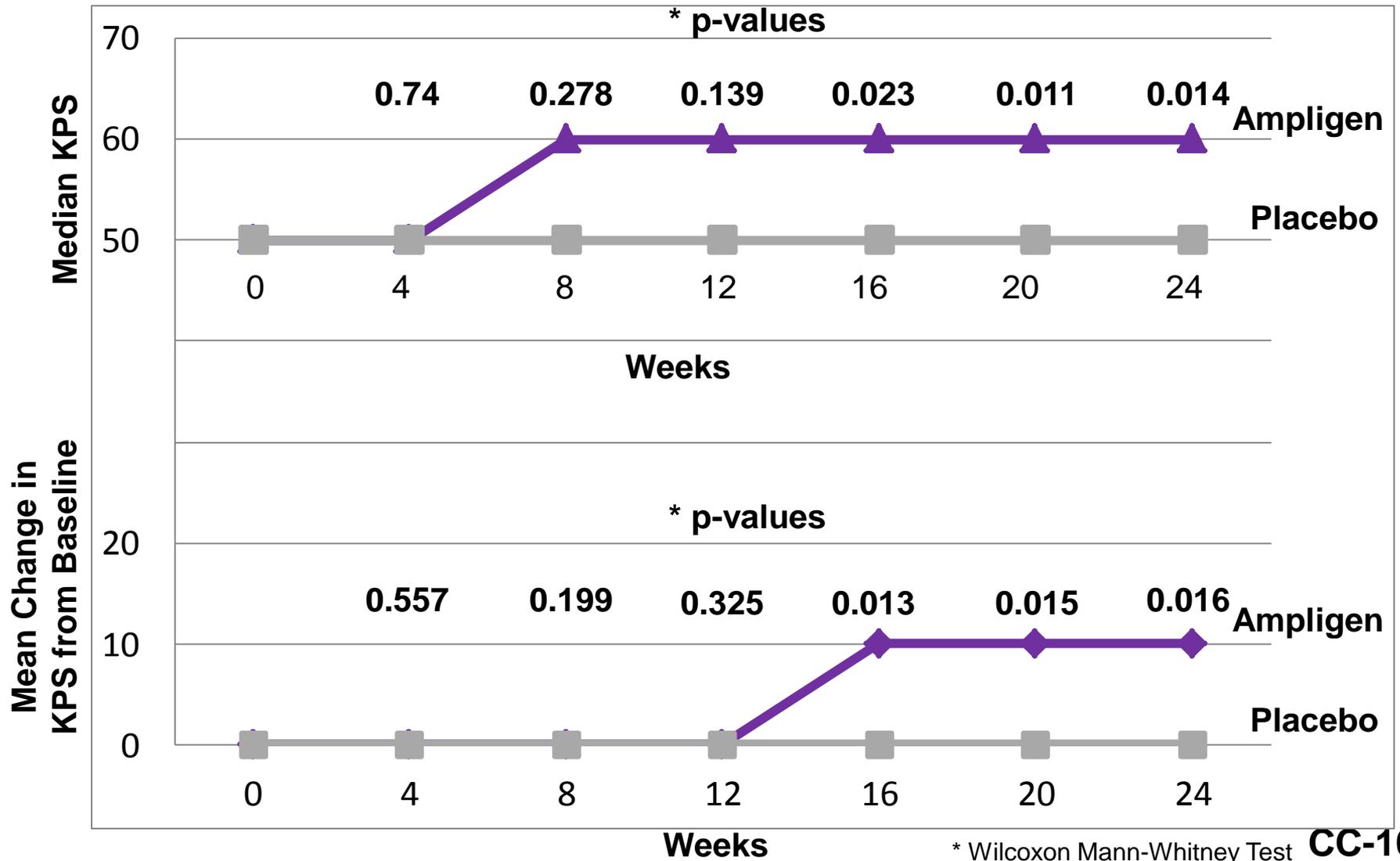
MCID = Minimal Clinically Important Difference, Samsa et al. *Pharmacoeconomics* 1999

Vitality is one of the best SF-36 scales for measuring the reduction in functioning seen in patients with CFS (Jason et al. *Disabil Rehabil* 2012)

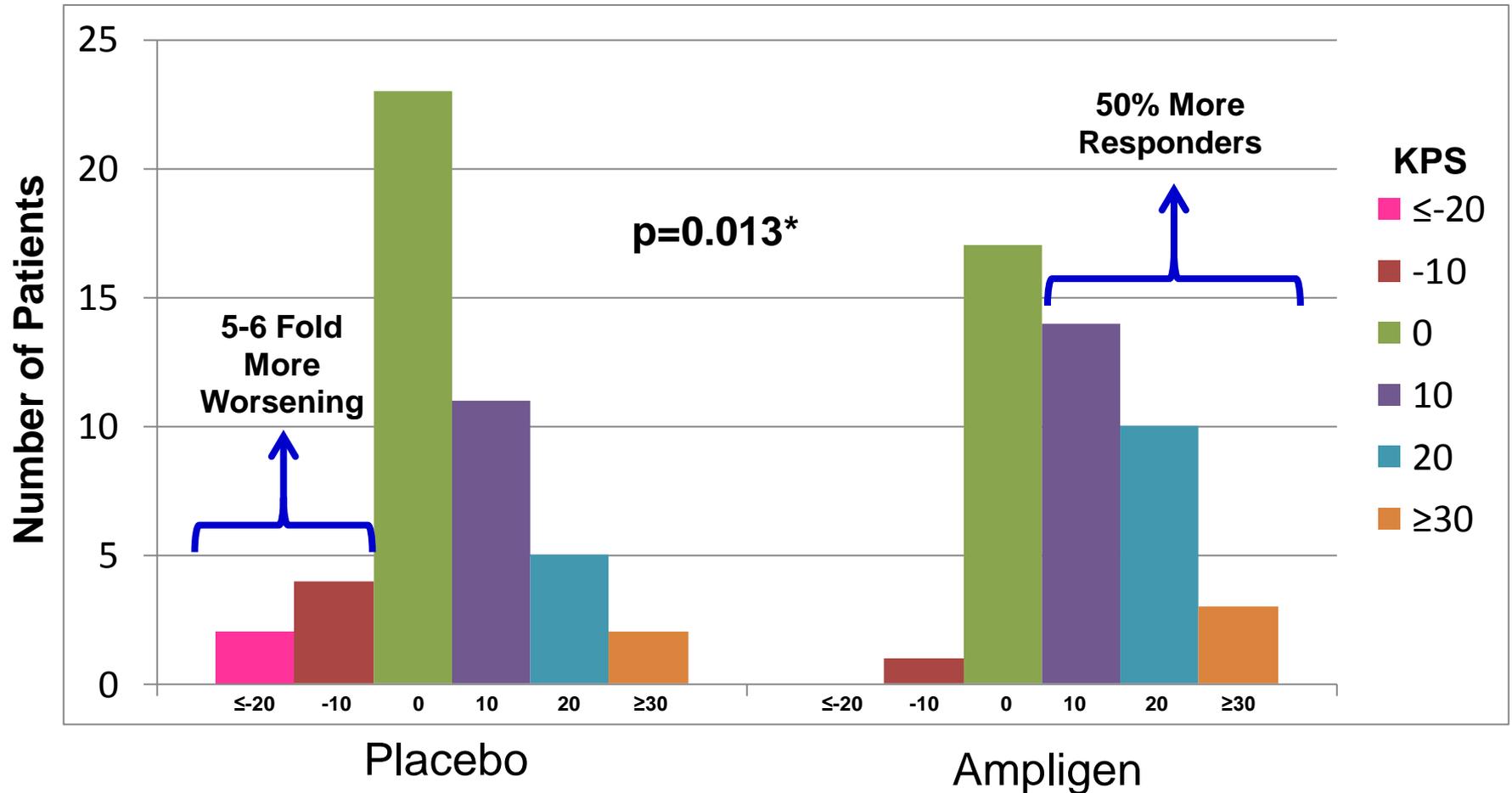
Well-Controlled Studies AMP-502 and AMP-516 Were Designed to Provide Complementary Clinical Insights

	AMP-502	AMP-516
Both Study Designs were Prospective, Randomized, Double-Blind, Placebo-Controlled, Multi-Center, with Equal Parallel Groups and Both Utilized a Central Laboratory	X	X
Utilized Ampligen at a Dosage Level of 400 mg given IV Twice Weekly vs. Placebo IV Twice Weekly	X	X
Enrolled Both Females and Males between the Ages of 18 – 60 with Severely Debilitating CFS	X	X
Utilized an Independent Team that Travelled to Each Site to Conduct the ETT Evaluations	X	X
ETT was the Primary Endpoint (AMP-516) and Secondary Endpoint (AMP-502)	X	X
KPS was the Primary Endpoint (AMP-502) and Secondary Endpoint (AMP-516)	X	X
Concomitant Medications Usage, and ADL were Secondary Endpoints	X	X

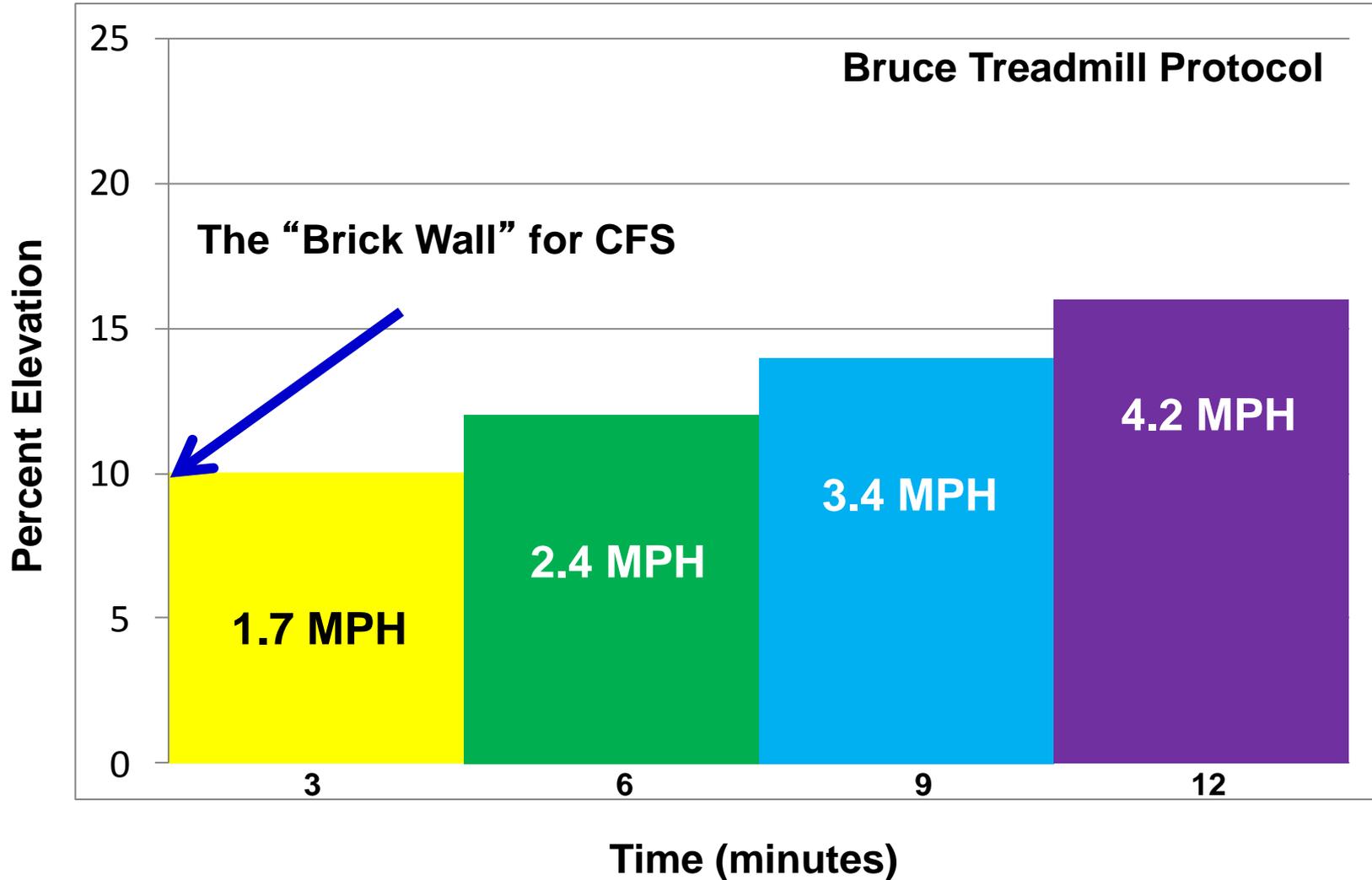
AMP-502: Median and Median Changes in KPS from Baseline to Week 24 Show Primary Endpoint was Met for ITT Population (Protocol-Driven Analysis)



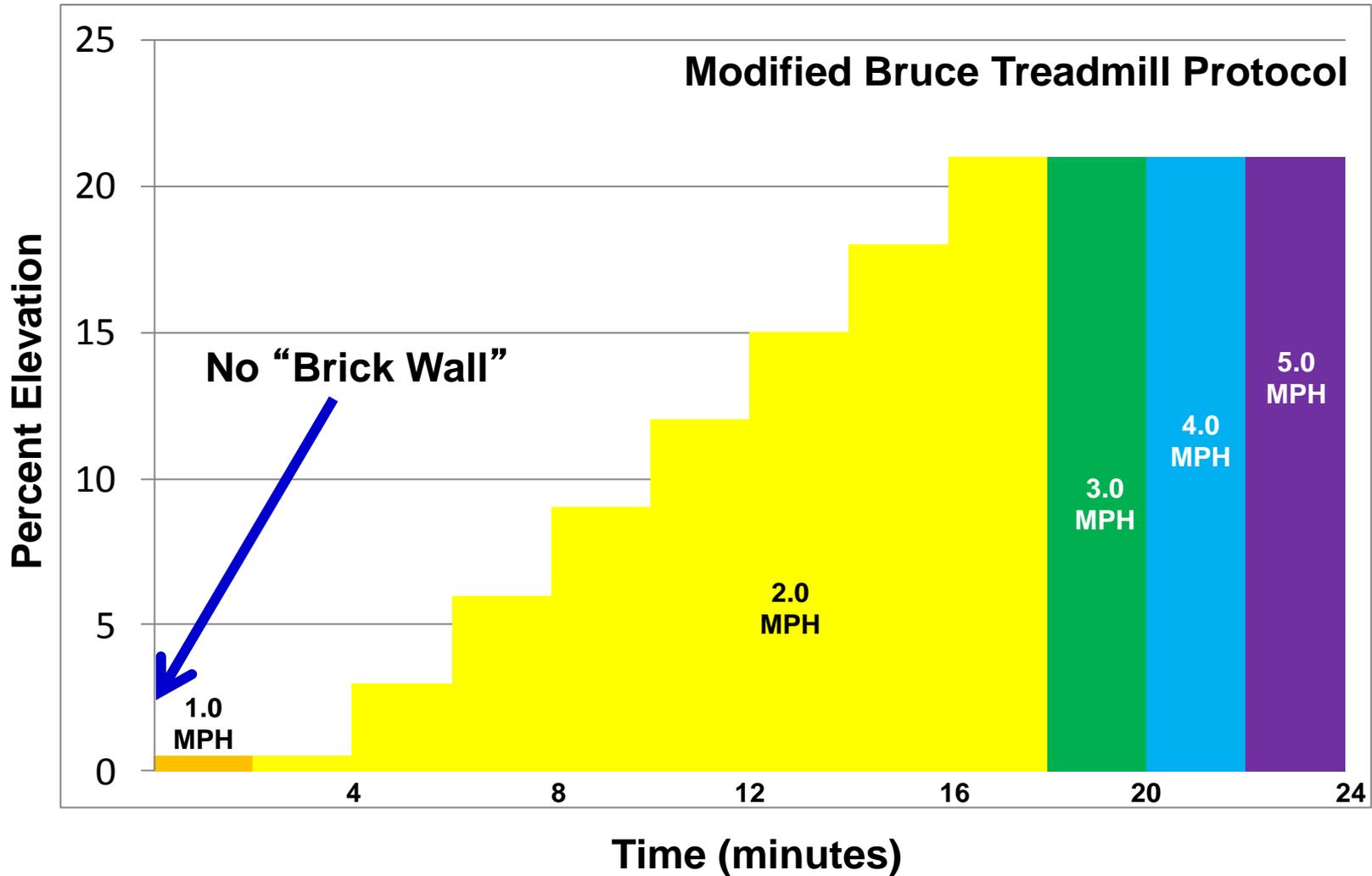
AMP-502: KPS Change from Baseline to Week 24 Shows Greater Improvement for Ampligen (ITT Population)



Initial Exercise Treadmill Schedule which was Too Rigorous for Severely Debilitated CFS Subjects



Modified Exercise Treadmill Protocol which was Needed for Severely Debilitated CFS Subjects



AMP-502: Intra-Group Change from Baseline in ETT Duration at Week 24

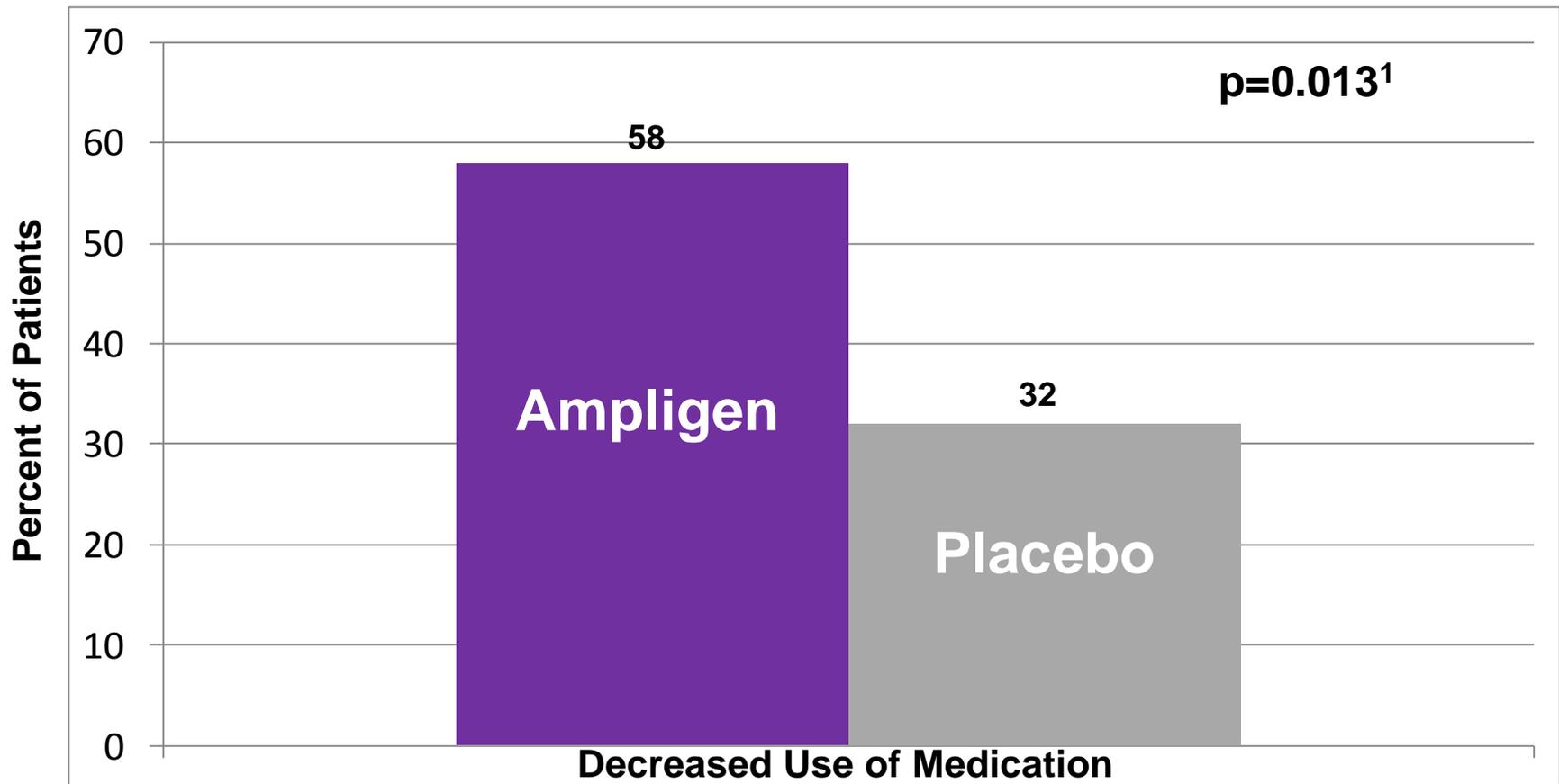
Sponsor Analysis	Ampligen	Placebo	p-value
Full Analysis Set, Excludes Seven (7) Patients ¹	n=41	n=44	
Mean Baseline - Seconds	744.1	602.8	
Mean Change from Baseline	95.3	57.9	0.010²
FDA Analysis	n=45	n=47	
Mean Baseline - Seconds	811	672	
Mean Change from Baseline	63	20	0.08³

¹ Includes all subjects who had a Gillespie modified Bruce protocol ETT at Baseline and had a minimum of one post-Baseline Gillespie modified Bruce protocol ETT evaluation

² An ANCOVA of log-ratio transformed data with Baseline and sites as covariates, mean adjusted by least square means

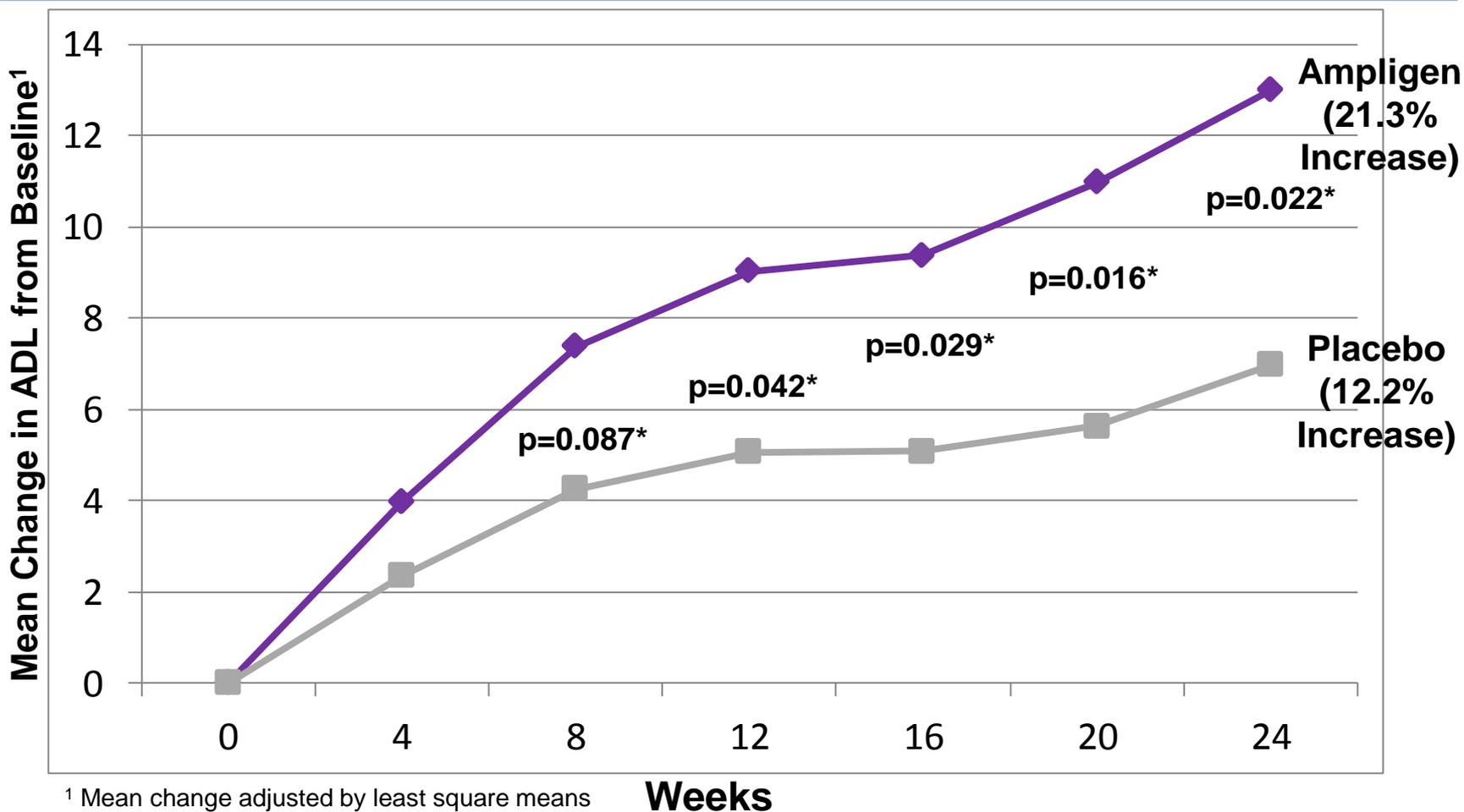
³ FDA analysis ANCOVA (LOCF), site in model using log transformed data

Change from Initial Use of Concomitant Medications in an Attempt to Palliate Symptoms of CFS Shows a Greater Decrease with Ampligen Compared to Placebo (ITT) (AMP-502)



¹ Chi-square test

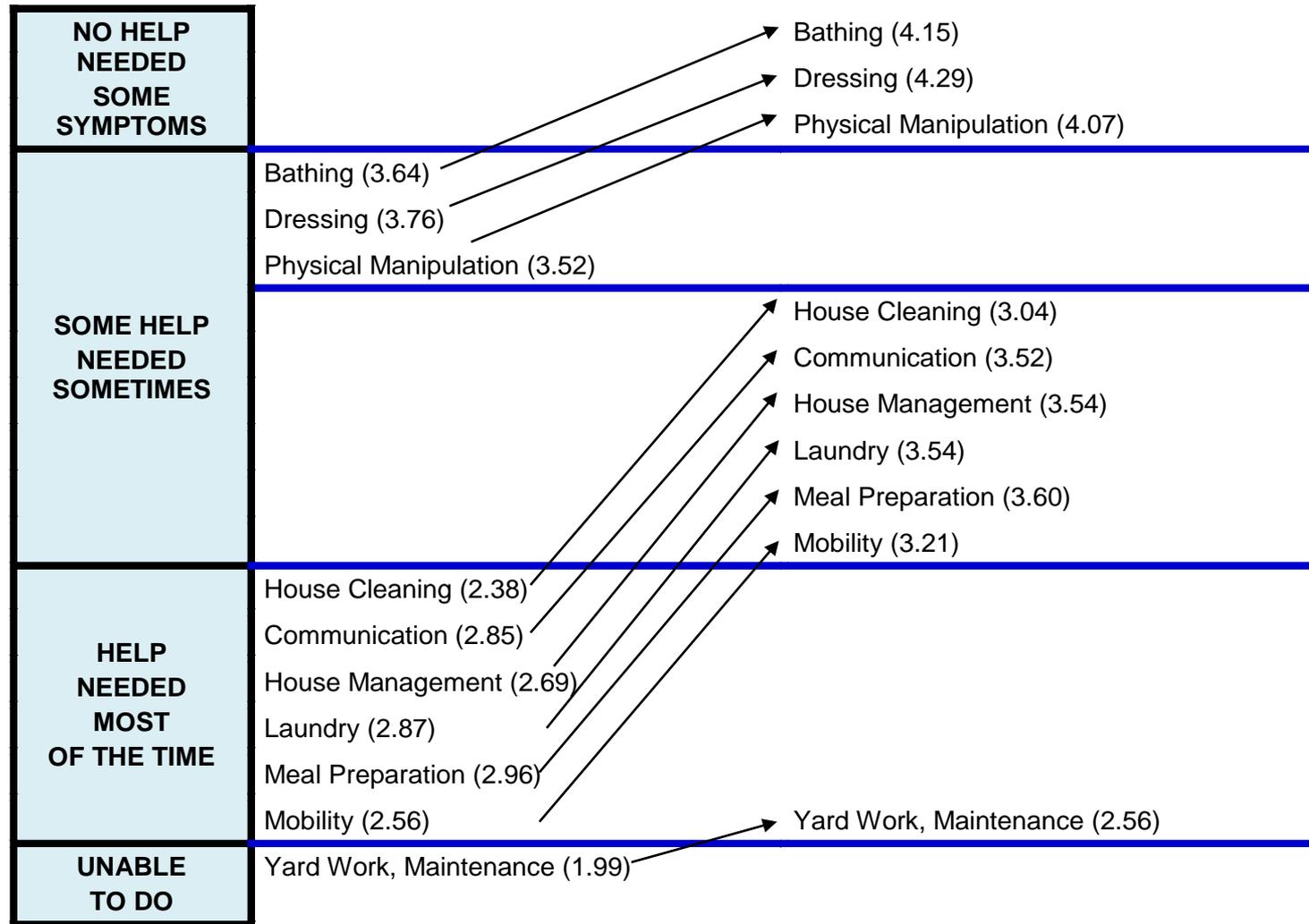
Mean Change from Baseline of Activities of Daily Living (ADL) Scores (ITT Population, Study AMP-502)



¹ Mean change adjusted by least square means

* An ANCOVA with baseline as covariate

Characterization of Improvements in Activities of Daily Living (All Patients Receiving Ampligen in AMP-502)



Efficacy Conclusions

1. Phase III Study (AMP-516)

- Primary endpoint (ETT) was met
- 25% increase in ETT is clinically meaningful
- Greater percentage of Ampligen patients increase by $\geq 25\%$ in ETT than placebo
- Concomitant medication use was decreased

2. Phase II Study (AMP-502)

- Primary endpoint (KPS) was met
- Secondary endpoints supports AMP-516

**William A. Carter, M.D.
Chief Executive Officer and
Chief Scientific Officer,
Hemispherx Biopharma, Inc.**

Summary Analysis of Risk Benefit of Ampligen

History of Ampligen Safety Reporting

- One hundred and eighteen reports were filed with Agency by Hemispherx between 1997 and December 20, 2012
- Thirteen field inspections were conducted by FDA between 1991 and 2012 regarding Ampligen clinical trials
- Original NDA filed in 2008 (CRL received 2009)
- No significant safety concerns were expressed between 1992 and 2012 by the Agency until closing months of 2012. More detailed review of CRFs will retire concerns

Safety Issues and Methodology of Assessment

Guidance	Issue	Sponsor's Perspective
1. Exposure Guidelines for New Drugs SAFETY	Drug exposure does not meet requirements for non-life-threatening condition	Drug meets exposure requirements for life-threatening diseases
2. Liver Injury Guidance SAFETY	Perception of permanent liver damage	Abnormalities transitory and manageable
3. Good Clinical Practice (GCP) Guidelines SAFETY	Single syndrome counted as multiple events	A single syndrome should be counted as single event
4. Appropriate Use of Medical Dictionary SAFETY	Benign tumors counted as malignancy	Lipoma is benign

Efficacy Summary

- Pivotal Study 516 Analysis of Primary Endpoint
 - Untransformed ETT data not skewed
 - Pre-specified Primary Endpoint met ($p=0.047$, untransformed)
- Key Secondary Efficacy Endpoints indicating clinical improvement:
 - Study 502 ETT met endpoint ($p=0.01$)
 - QoL/Symptom Burden Measures all-positive – KPS (AMP-502) and secondary endpoints support AMP-516
- Reduction of concomitant medications (i.e., symptom-directed therapies)
 - **Reduced polypharmacy**
 - **Reduced use of QT prolonging drugs**
- **CFS disease progression is mitigated**

Safety Summary

- Liver function tests (≥ 3 ULN, SGPT)
 - Transitory increase, only one discontinuation secondary to LFTs
- Local infusion site reactions – most were mild to moderate (0.03% of total infusions resulted in a severe reaction)
 - 44,054 infusions resulted in only 2 discontinuations
- Systemic infusion reactions – most were mild to moderate flu-like symptoms (11% (Ampligen) vs. 7.5% (placebo) were severe)

Safety Summary - continued

- No QTc interval prolongation observed
- Higher rate of QT prolongation in placebo
- No increase in deaths/suicides in controlled studies
 - 3 deaths in open-label study, within expected rate
- No increase in SAEs in controlled studies

Ampligen Mitigates CFS Progression

	Ampligen	Placebo	p-value
≥50% Decrease ETT (ITT Population with >9 Minute Subset)	0%	9.1%	<0.001
≥10 Points Decrease in KPS	2.2%	13%	<0.013
ETT Change (ITT Population with >9 Minute Subset)	+73 seconds	-13 seconds	0.0264

Key Cardiac Toxicity Results Evidencing a Consistent Protective Advantage of Ampligen Over Placebo

	Placebo	Ampligen
QTc Prolongation Mean	Mean Increase ≥5 Milliseconds	Mean Increase <5 Milliseconds

Relative Therapeutic Advantage: Ampligen vs. Current Standard of Care in Distinct Therapeutic Categories

	Ampligen
Core Fatigue* Decrease	✓
Improve Activity Performance ($\geq 25\%$ ETT) **	✓
Global QOL* Increase	✓
Polypharmacy* Reduction	✓
EKG Selected Risk(s) ** Decrease	✓
Decrease in CFS Disease Progression*	✓
No Increase in Suicide*	✓
No Increase in SAE or Hospitalizations**	✓
No Increase in Autoimmunity*	✓

*Protocol-Driven Analysis

**Post-hoc Analysis

“I have been administering Ampligen to patients for the last 24 years. I would tell you my experience with Ampligen has been good. We have had patients across the spectrum from remarkable to modest improvements. And for those who it did not work, it did no harm. I cannot recall anyone who got worse on Ampligen.”

Dr. Lapp’s experience based on approximately 24,000 CFS patient consultations over 2.4 decades

Charles W. Lapp, MD

Director, Hunter-Hopkins Center, Charlotte, North Carolina

Assistant Consulting Professor at Duke University Medical Center

Diplomate, American Board of Internal Medicine

Fellow, American Board of Pediatrics

Robert Miller
CFS Patient
Currently on Ampligen
CFS Patient
Advocacy Group

Summary of Benefit-Risk Assessment Relative to Current Standard of Care: Analyzing Ampligen for Severely Debilitating CFS

Consideration	Favorable Benefit-Risk
Severe Condition	Yes
Unmet Medical Need	Yes
Clinical Benefit	Yes
Acceptable Risk	Yes

Excerpted public presentation by Dr. John Jenkins, CDER

AMP-502 Trial is a Pivotal, Not Hypothesis Generating, Trial

- FDA now asserts study was flawed because of reducing duration of study from 48 to 24 weeks, which FDA believes would “usually” necessitate an **unblinding** of study. This is incorrect.
- Sponsor’s decision to decrease duration of endpoint in fact resulted from evaluation of the standard deviation combined with a hypothetical effect size which could be detected with a smaller standard deviation. **Thus, the treatment group assignments remained blinded and were not used in this exercise. The blind was not broken until the end of study.**

Categories of Concomitant Medications Used to Treat Symptoms Associated With Chronic Fatigue Syndrome as Defined by the Centers for Disease Control and Prevention

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Sleep Disturbances	Sedatives, Hypnotics, Analgesics, Narcotics

AMP 502 Symptom Checklist-90 Scores

Another of the protocol-defined secondary efficacy endpoints was improvement from baseline to Week 24 in SCL-90-R CD score, statistically significantly greater in the Ampligen group than in the placebo group.

There was a statistically significant ($p=0.036$) improvement in mean change in SCL- 90-R CD scores from baseline to Week 24 in the Ampligen group compared with the placebo group.

AMP-502 Mean Changes in SCL-90-R-CD Cognitive Deficit (CD) Subscale Score During Study (ITT)							
Cognitive Ability	n	Ampligen		n	Placebo		p-value**
		Mean	% Improved		Mean	% Improved	
Change at Week 24 Relative at Baseline*	43	-0.72	28.5	44	0.40	15.9	0.036

*Week 24 minus Baseline adjusted for Baseline and center effects

**ANCOVA with Baseline and centers as covariates

Protocol designed secondary endpoint