



Immunology for a Better Future

A photograph of a pharmaceutical production line. Several glass vials with white caps are moving along a blue conveyor belt. The background is slightly blurred, showing more of the factory environment.

Ampligen: A General Overview and the Plan for ME/CFS and Long Covid

January 27, 2022

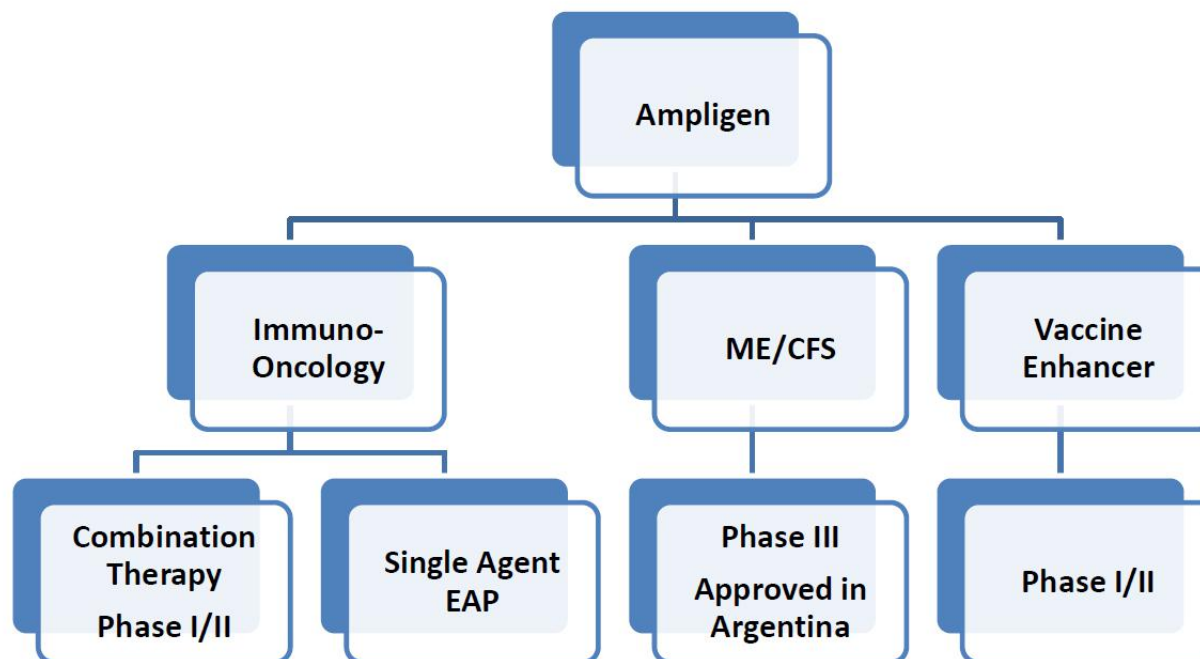
Forward-Looking Statements

Some of the statements included in this presentation may be forward-looking statements that involve a number of risks and uncertainties. Among other things, for those statements, AIM claims the protection of safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995. Any forward-looking statements set forth in this presentation speak only as of the date of this presentation. AIM does not undertake to update any of these forward-looking statements to reflect events or circumstances that occur after the date hereof. This presentation relates to clinical development plans for AIM's Ampligen for the treatment of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and Long COVID. These developments are subject to change for a number of reasons. AIM has been focusing on the use of Ampligen for the treatment of ME/CFS for a number of years. Ampligen is approved for commercial sale in the Argentine Republic for the treatment of severe Chronic Fatigue Syndrome, but commercial sales have not yet begun. In the U.S., the FDA issued a complete response letter ("CRL") in 2013 to AIM's New Drug Application and has requested additional trials and other information before it can proceed. AIM is working on a comprehensive follow through with the FDA. AIM learned a great deal since the FDA's CRL and plans to adjust its approach to concentrate on specific ME/CFS symptoms. Responses to the CRL and a proposed confirmatory trial are being worked on now by AIM's R&D team and consultants. The FDA authorized an open-label treatment protocol ("AMP-511") in a study under which severely debilitated CFS patients have the opportunity to be on Ampligen to treat this very serious and chronic condition. The AMP-511 protocol is ongoing. In October 2020, AIM received Institutional Review Board approval for the expansion of the AMP-511 protocol to include patients previously diagnosed with SARS-CoV-2 following clearance of the virus, but who still demonstrate chronic fatigue-like symptoms (Long COVID). Significant additional testing and trials will be required to determine whether Ampligen will be effective in the treatment of Long COVID. In addition, results obtained in animal models do not necessarily predict results in humans. Human clinical trials will be necessary to prove whether Ampligen will be efficacious in humans. No assurance can be given as to whether current or planned clinical trials will be successful or yield favorable data and the trials are subject to many factors including lack of regulatory approval(s), lack of study drug, or a change in priorities at the institutions sponsoring other trials. In addition, initiation of planned clinical trials may not occur secondary to many factors including lack of regulatory approval(s) or lack of study drug. Even if these clinical trials are initiated, AIM cannot assure that the clinical studies will be successful or yield any useful data or require additional funding. No assurance can be given that future studies will not result in findings that are different from those reported in the studies referenced in the presentation.

Please review the "Risk Factors" section in AIM's latest annual report on Form 10-K and subsequent quarterly reports on Form 10-Q. AIM'S filings are available at www.aimimmuno.com. The information found on AIM's website is not incorporated by reference into this presentation and is included for reference purposes only.

Ampligen (Rintatolimod) is a Broadly Applicable Immune Therapy

- Ampligen is a broadly applicable immune therapy that has the potential to be used in a wide range of indications
- Generally well-tolerated with over 100,000 IV doses in humans
- Ampligen has Orphan Drug Status in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Metastatic Melanoma, Renal Cell Carcinoma, and HIV in the US and Pancreatic Cancer and Ebola Virus Disease in the EU



Ampligen (Rintatolimod) Development Pipeline

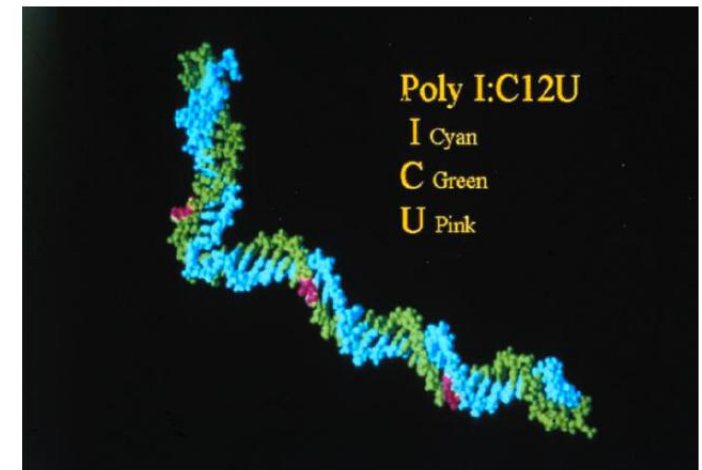
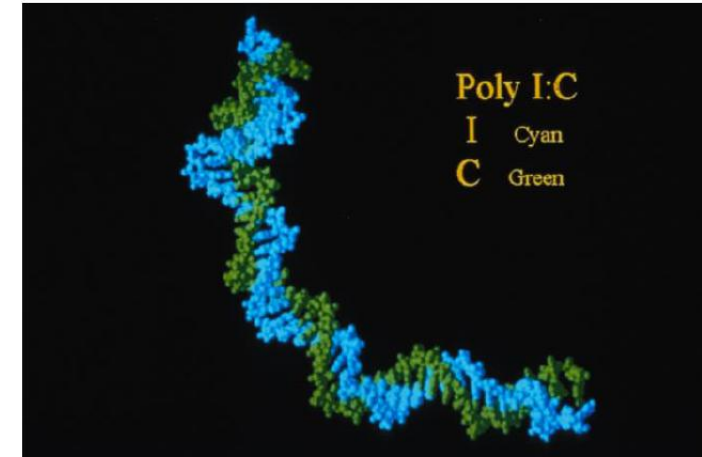
Disease / Indication	Pre-clinical	I	Phase II	III	NDA	Approved	EAP ¹
Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome*	●	●	●	●	US	Argentina	●
Ovarian, Colorectal, Renal Cell Carcinoma*, Prostate, and Melanoma* Cancers	●	●	●				
Breast Cancer	●	●					
Pancreatic Cancer	●						●
Bladder Cancer	●						
Vaccine Adjuvant (Influenza including highly pathogenic)	●	●	●				
HIV Disease*	●	●	●				

¹ EAP = Expanded Access Program / Early Access Program

* Orphan Drug Indications in US

Clinical Safety Profile Related to Molecular Structure of Ampligen (Poly I: Poly C₁₂U)

- Mis-paired regions of base pair hydrogen bonding accelerate chain hydrolysis while preserving biological activity
- Decreased toxicity and improved safety compared to the absence of mis-pairing
- No development of antibodies to Ampligen - In contrast to 40-60% antibody formation with poly ICLC and poly ICL [J. of IFN Research 3,281 (1983)]
- Ampligen is a selective TLR3 agonist compared to poly IC which also activates helicases (i.e. MDA-5)



Drug Product Characteristics

Ampligen (Poly I : Poly C₁₂U)

- Preparation: Liquid ready for Infusion
- Routes of Administration: intravenous (IV) infusion (over 30 minutes), intraperitoneal (IP), and intranasal (IN)
- Half-life: approximately 40 minutes (IV)
- Dose regimen: 400 mg twice weekly (IV)
- Blood level: peak concentration 50-60 µg/ml (IV)

Ampligen Exposure

- Ampligen has been generally well-tolerated in clinical trials enrolling:
 - >1200 patients total (all indications)
 - >800 patients with CFS, and
 - Over 100,000 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 needed for NON-LIFE threatening conditions: *FDA Guidance for Industry: Premarketing Risk Assessment*, March, 2005

Ampligen (Rintatolimod) Mechanism of Action

- Ampligen is unique amongst TLR agonists in its mechanism of action, specificity and safety profile
- Only TLR to exclusively activate the TRIF adaptor and avoids the more inflammatory MyD88 pathway used by all other TLR agonists
- Ampligen is the only TLR3 agonist to avoid helicase activation of NF- κ B. Natural dsRNAs and poly IC which activate NF- κ B in the tumor microenvironment (TME) \uparrow Tregs and have the potential to enhance cancer cell proliferation (Theodoraki, et al. 2018)
- Ampligen induces a wide range of immunologic / antitumor activities

The Immunological Activity of Ampligen has been Demonstrated in a Wide Body of Literature

Immunological Activity	Reference(s)*
Only TLR3 agonist to promote selective attraction of CTLs (Teff) with concomitant increase in Teff/Treg ratio in the TME	Theodoraki, et al. (2018)
Ampligen induces desirable chemokines in the TME, while other TLR3 agonists, such as poly IC, by activating helicases, induce tumor-promoting signals	Theodoraki, et al. (2017)
Phase I/II colorectal cancer trial of Ampligen plus rIFN α -2b and celecoxib showed increase ratio of CXCL10 (CTL-attractant) to CCL22 (Treg-attractant) and increase ratio of CTL/Treg markers	Kalinski, et al. (2016)
Induces epitope spreading and cross-reactive IgA antibody formation in humans with well-tolerated safety profile of intranasal Ampligen	Overton, et al. (2014)
dsRNA/Ampligen increased activity (synergistically) of anti-PD1/PD-L1 drugs	Nagato, et al. (2014); Celis Unpub Data
↑ Teff-attracting chemokine (CXCL10) in the tumor microenvironment (TME)	Muthuswamy, et al. (2012); Kalinski Unpub. Data

* Full reference citations available upon request

The Immunological Activity of Ampligen has been Demonstrated in a Wide Body of Literature – *cont'd*

Immunological Activity	Reference(s)*
Induces dendritic cell maturation: Enhances bioactivity of cancer immunotherapy	Nicodemus, et al. (2010)
Promotes optimal dendritic cell maturation and Th1-type responses of healthy donors and cancer patients <i>in vivo</i>	Navabi, et al. (2009)
Induces epitope spreading and/or cross-protective immunity in mice and monkeys	Ichinohe, et al. (2007) Ichinohe, et al. (2010)
Increases Delayed Type Hypersensitivity (DTH) response in HIV disease	Thompson, et al. (1996)
Increases LAK cytotoxicity	Hubbell, et al. (1992b)
Increases antitumor immune mechanisms and survival in animal models of renal cell carcinoma and melanoma	Hubbell, et al. (1992a); Hubbell, et al. (1990)
Induction of macrophage tumoricidal activity	Pinto, et al. (1988)
Increases Natural Killer (NK) cell activity	Zarling, et al. (1980)

* Full reference citations available upon request

Overview of Chronic Fatigue Syndrome

- Severely debilitating, progressive disease
- Effects multiple organ systems
 - >1 million diagnosed cases in U.S.
 - ~60-80% severely afflicted (~700,000)
- CDC: Chronic Fatigue Syndrome (CFS) is as debilitating as Multiple Sclerosis (MS), Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA)
- Most CFS patients have been ill >5 years
- Substantially unmet medical need
- Only approved therapy: Ampligen in Argentina for severe CFS

Overview of Ampligen's Safety Profile

- Administered by intravenous (IV) infusion over 30 to 60 minutes
- Generally well-tolerated
- Extensive exposure to drug (>600 patient treatment years), including two placebo-controlled pivotal studies
- Favorable safety profile overall and specifically for the QT Interval, Autoimmunity, Hospitalization for Depression/Suicide Attempt, and Cancer
- Most frequent adverse event is a flu-like syndrome that is usually mild and short-lived consisting of headache, chills, fever, flushing, and myalgia
- This CFS specific treatment allows for reduction in symptom directed therapy (e.g. current standard of care)

Clinical Safety Record of Ampligen (dsRNA)

- The Ampligen serious adverse event (SAE) profile shows no difference compared to placebo
- An FDA CFS Advisory Committee voted in favor of its clinical safety for commercial use
- No evidence of autoimmunity in >100,000 drug administrations

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

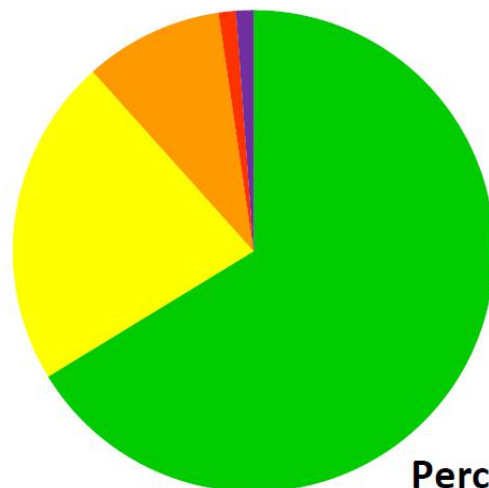
Relationship to Study Drug	Number of Serious Adverse Events	
	Ampligen	Placebo
Not Related	16	16
Remote	4	3
Possible	2	2
Probable	0	1
Definite	0	0
Total	22	22

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

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

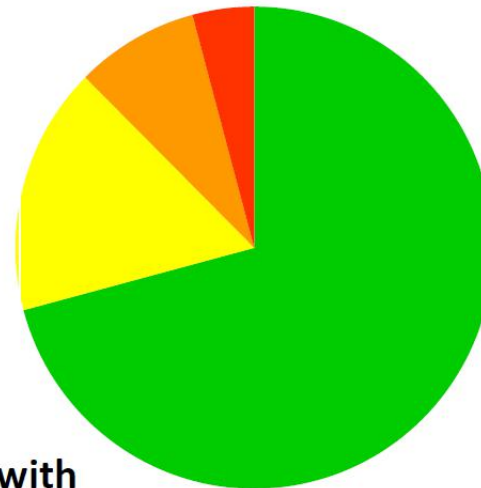
All CFS Studies²

Ampligen Group



7.7%

Placebo Group



8.6%

Percent of Patients with
SAEs

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

Safety Findings from Two Well-Controlled Pivotal Studies (502 and 516)

- No Evidence of new Autoimmune Disease
- No Evidence for Induction of Autoantibodies
- No Increase of Treatment Emergent Depression or Suicide Attempts
- No Increase Incidence of Cancer
- 5.6 % increase in SGOT (AST) or SGPT (ALT) >3 times ULN was managed by dose reductions and did not result in any study discontinuations
- No increase in Serious Adverse Events (SAEs)
- No Increase in QT Interval
- No Deaths

Overview of Ampligen's Efficacy in ME/CFS

1. Phase III Study (AMP-516)

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

2. Phase II Study (AMP-502)

- Primary endpoint: Karnofsky Performance Score (KPS) was met
- Secondary endpoints support AMP-516

AMP-516 Phase III Study Design

- Randomized, Placebo-controlled
- 40 weeks of Double-Blinded Treatment (Stage 1)
- Ampligen Dose = 400 mg or placebo
- Twice weekly IV infusions
- Primary Endpoint: Exercise Treadmill Tolerance (ETT)
- **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 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		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**

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

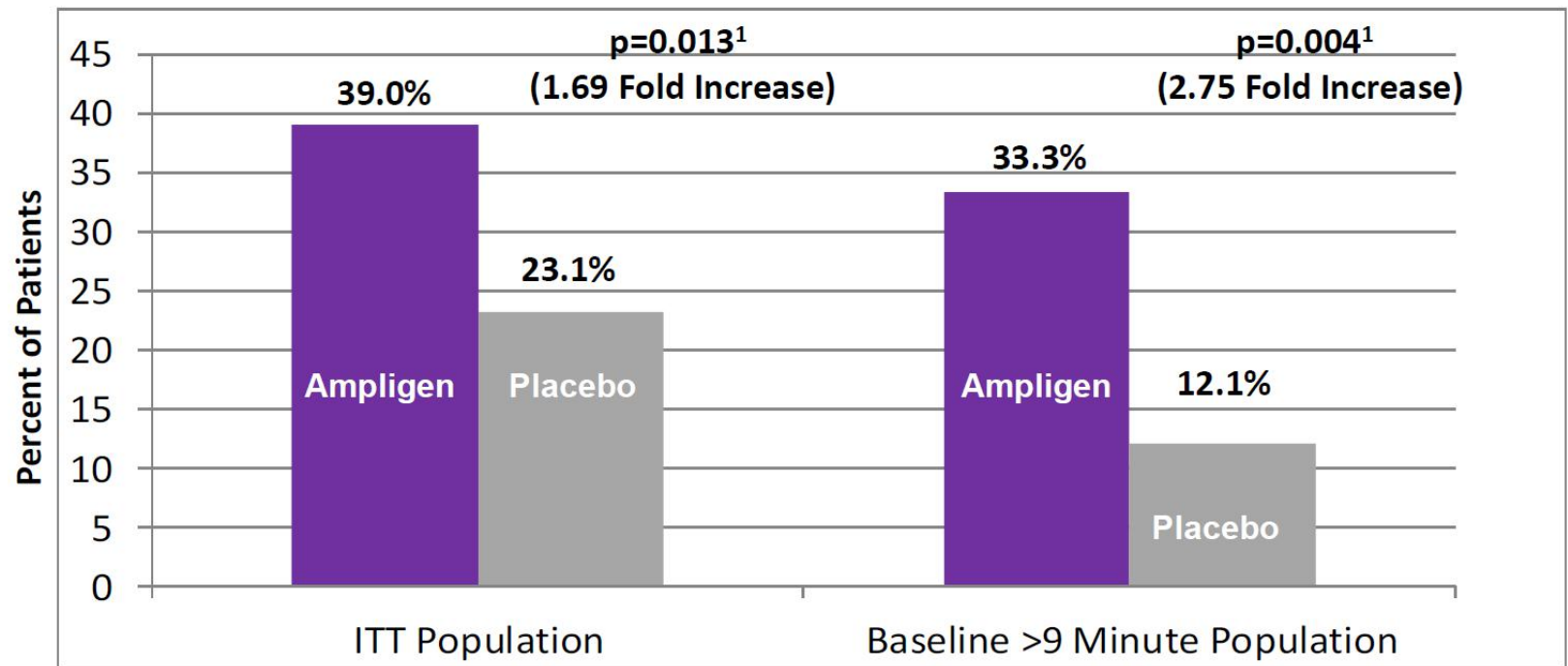
¹ Analysis of Covariance (Baseline as Covariate) non-transformed ETT data

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

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**

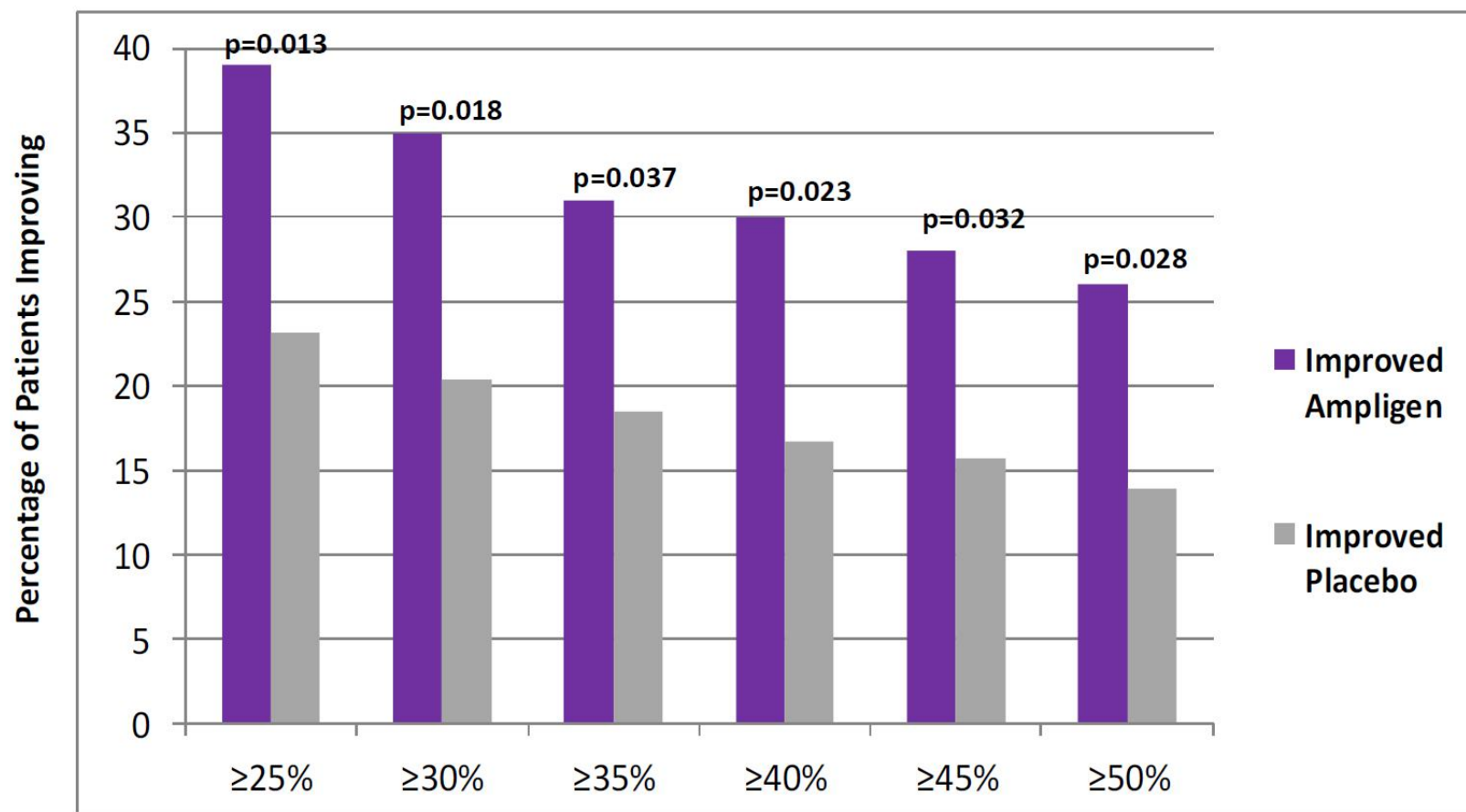
AMP-516: Clinical Relevance of at Least a 25% Increase in ETT from Baseline. Greater Improvement with Ampligen Compared to Placebo



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

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

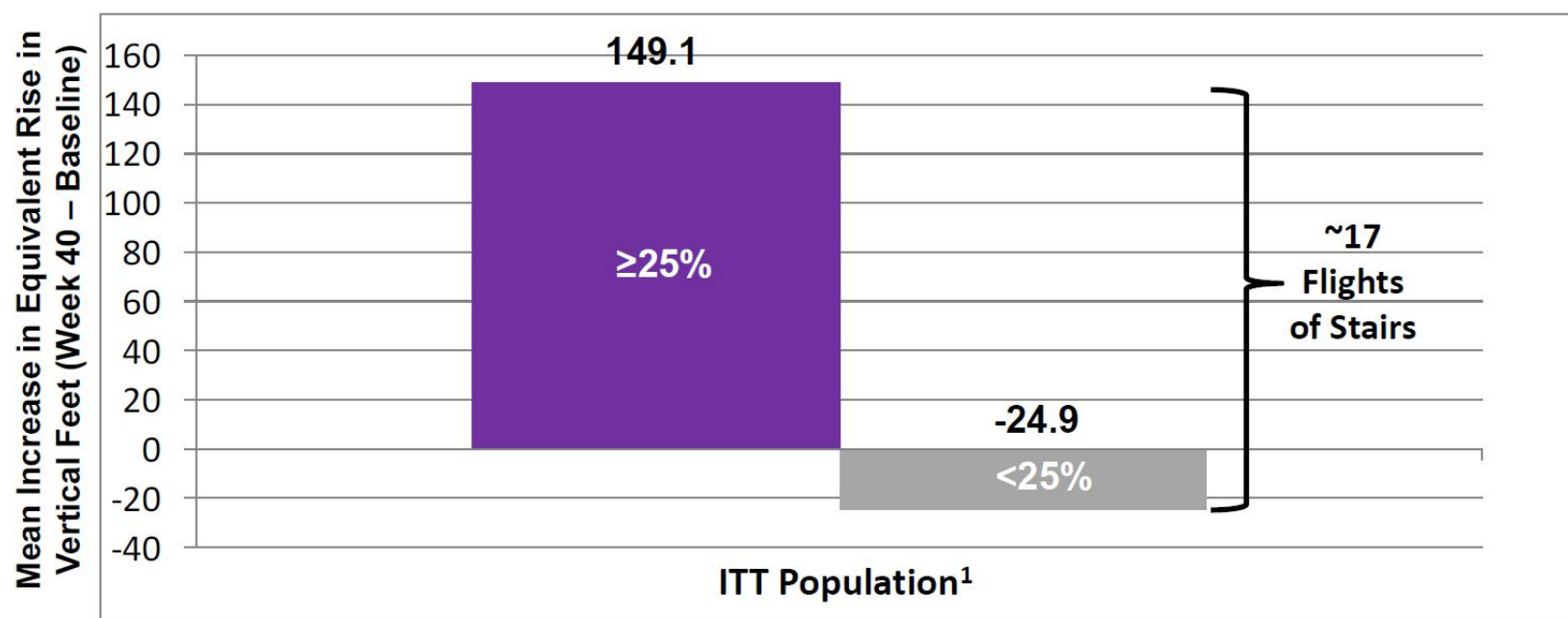
Dichotomizing the Ampligen Treated ITT Population Based on Significant Clinical Improvement ($\geq 25\%$) at Week 40 in ETT Duration Shows There is Corresponding Clinically Significant Improvements in Secondary Endpoints, KPS and Vitality (SF-36) for the $\geq 25\%$ ETT Improving Ampligen Cohort

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

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

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

AMP-516: Ampligen Treated Patients by ETT Response ($\geq 25\%$ vs. $< 25\%$) Comparison of Change from Baseline in Vertical Rise During ETT at Week 40 for ITT Population



¹ In the ITT population, the difference between ETT responders ($\geq 25\%$ increase) and non-responders ($< 25\%$ increase) was that ETT responders had an ability to climb an equivalent of ~17 more flights of stairs or ~170 vertical feet more than the non-responders.

**Identification of a Subset of AMP-516
CFS Patients with Twice the Response
Rate with Regard to the Primary Endpoint
Exercise Treadmill Tolerance (ETT)
Compared to the ITT Population**

Definition of the AMP-516 Target Subset (n=75)

Target Population consists of the subset of the AMP-516 ITT Population (n=208) with:

1. Onset of symptoms of CFS between 2 and 8 years before enrollment into the trial
2. Post-exertional malaise (PEM) lasting ≥ 24 hours
3. Ability to walk on moving treadmill (grade 0% and belt speed = 1 mph) at least one, but not over 16 minutes

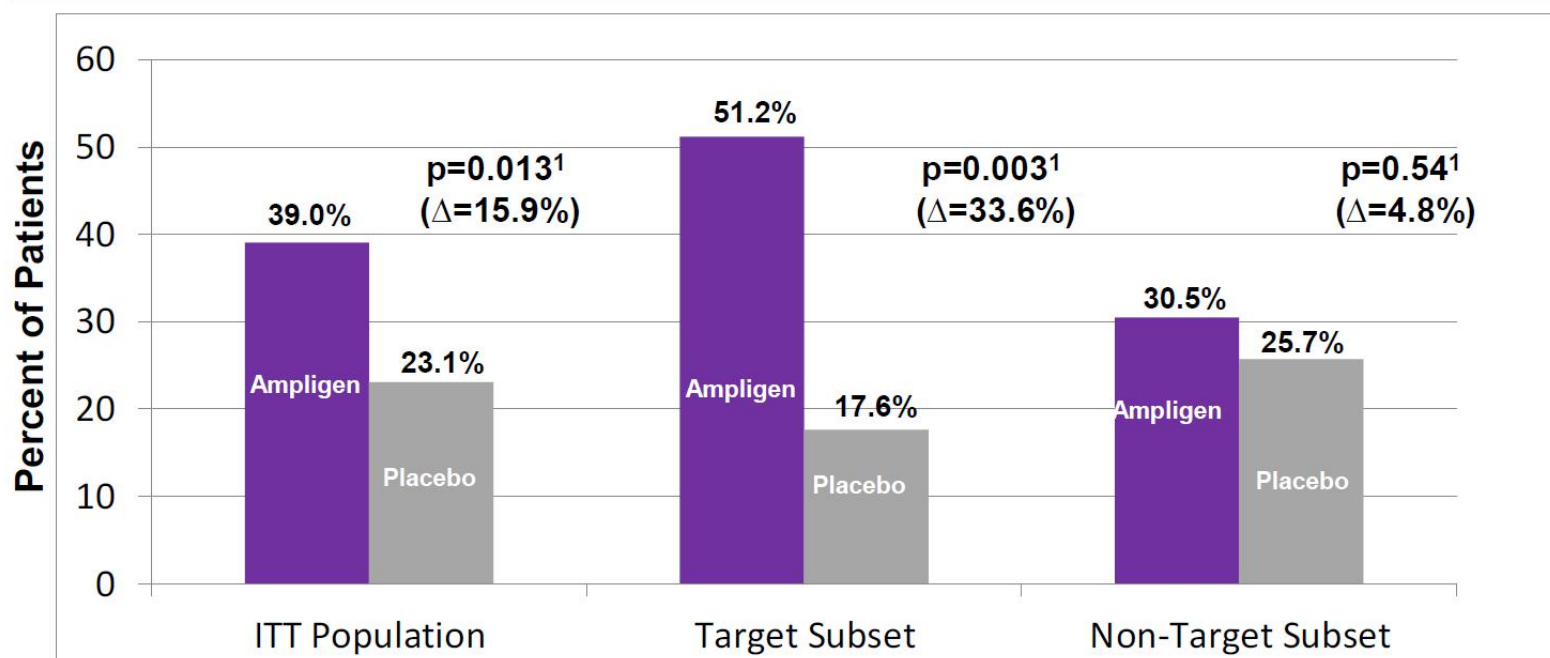
Note: Mean duration of CFS Symptoms was 9.5 years for the Ampligen patients vs. 9.7 years for placebo patients, enrolled in AMP-516.

Definition of Non-Target Subset (n=133)

Non-Target Population consists of the subset of the AMP-516 ITT Population that did not meet the definition of the Target Subset.

Note: Total ITT Population (n=208).

AMP-516: Percent of Patients with at Least a 25% Increase* in ETT from Baseline; Greater Improvement with Ampligen Compared to Placebo



¹ p-values derived from Chi-squared test

* 25% increase based on a request from FDA (Division of Antiviral Drug Products – March 1997) to establish a meaningful percent change that is above intra-patient ETT Variability

Ampligen (rintatolimod) for CFS: Summary

- Ampligen (rintatolimod) is the only investigational drug treatment for CFS which has completed two pivotal clinical trials and has an active CFS NDA with FDA
- Has Orphan Drug Designation for CFS and an ongoing Treatment Protocol (CFS) authorized by the FDA
- Has received an FDA CFS Advisory Committee vote in favor of its clinical safety for commercial use
- Has an approval for the severe CFS indication (Republic of Argentina, 2016)
- Developing protocol for confirmatory Phase 3 trial, required for U.S. NDA

Post-COVID Conditions*

- Other names for Post-COVID Conditions
 - Long COVID
 - Long-haul COVID
 - Post-acute COVID-19
 - Long-term effects of COVID
 - Chronic COVID

* CDC Website September 16, 2021 [Post Covid Conditions](#)

Post-COVID Conditions*

- Characteristics of Post-COVID Conditions
 - Most people with COVID-19 get better within weeks of illness onset
 - However, some experience “Post COVID Conditions”
 - Even asymptomatic people with COVID-19 can develop Post-COVID conditions

* CDC Website September 16, 2021 [Post Covid Conditions](#)

What are Post-COVID Conditions?

- Post-COVID conditions are a wide range of new ongoing health problems experienced four or more weeks after the initial infection with the SARS-CoV-2 virus
- Current list of CDC Post-COVID Conditions:
 - Difficulty breathing or shortness of breath
 - Tiredness or fatigue
 - Symptoms that get worse after physical or mental activities (also known as post-exertional malaise)
 - Difficulty thinking or concentrating (sometimes referred to as “brain fog”)
 - Cough
 - Chest or stomach pain
 - Headache
 - Fast-beating or pounding heart (also known as heart palpitations)
 - Joint or muscle pain
 - Pins-and-needles feeling
 - Diarrhea
 - Sleep problems
 - Fever
 - Dizziness on standing (lightheadedness)
 - Rash
 - Mood changes
 - Change in smell or taste
 - Changes in menstrual period cycles