A Multi-Center, Phase IIb, Randomized, Placebo-Controlled, Double-Blind Study Of The Effects Of N-Acetylcysteine (NAC) On Redox Changes And Lung Inflammation In Cystic Fibrosis Patients.

Lead Site: Stanford University - Carol Conrad, MD and Rabin Tirouvanziam, PhD

Participating sites:

University of Utah – Barbara Chatfield, MD
Birmingham Children's Hospital – J.P. Clancy, MD
Yale University – Marie Egan, MD
Duke University – Peter Michelson, MD
National Jewish Hospital – David Nichols, MD
Columbia University – Lynne Quittel, MD
Children's Hospital of Philadelphia – Ron Rubenstein, MD
Children's Hospital of Pittsburgh – Jonathan Spahr, MD
Penn State, Hershey – Robert Vender, MD
University of Florida, Gainesville – Veena Antony, MD

Effects of NAC on Redox Changes and Lung Inflammation

- Hypothesis: GSH replenishment to blood neutrophils will allow for a decrease neutrophil inflammation in the sputum of CF subjects as determined by sputum elastase activity.
- Oral NAC fizzy tablets, 900 mg PO TID, or placebo
  - Primary efficacy measures: sputum elastase activity (ELISA)
  - Secondary efficacy measures: FEV_1 (% pred.)
- Sputum, blood, PFT's, and QOL on Day 0 and Week 6, Week 12, and Week 24.

Phase IIB Proof of Concept

- Staged enrollment, Stanford first cohort
  - In-depth studies to assess if any potential for pulmonary hypertension
  - 16 subjects completed study
    - No AE's related to NAC
    - No PH (detected by ECHO, DLCO, no free NAC in plasma, no S-nitrosylated NAC detected in plasma)
- Other sites initiated in November 2009
  - 11 sites/80 subjects planned/ 70 enrolled
  - Smaller panel PH studies

Secondary Objectives

- Eval effect of NAC on number of pulmonary and sinus exacerbations, antibiotic use
- Eval effect of NAC on inflammation in the lungs (neutrophil count)
- Eval effect of NAC on pulmonary function
- Eval effect of NAC on weight
- Eval effect of NAC on QOL

Safety Objectives

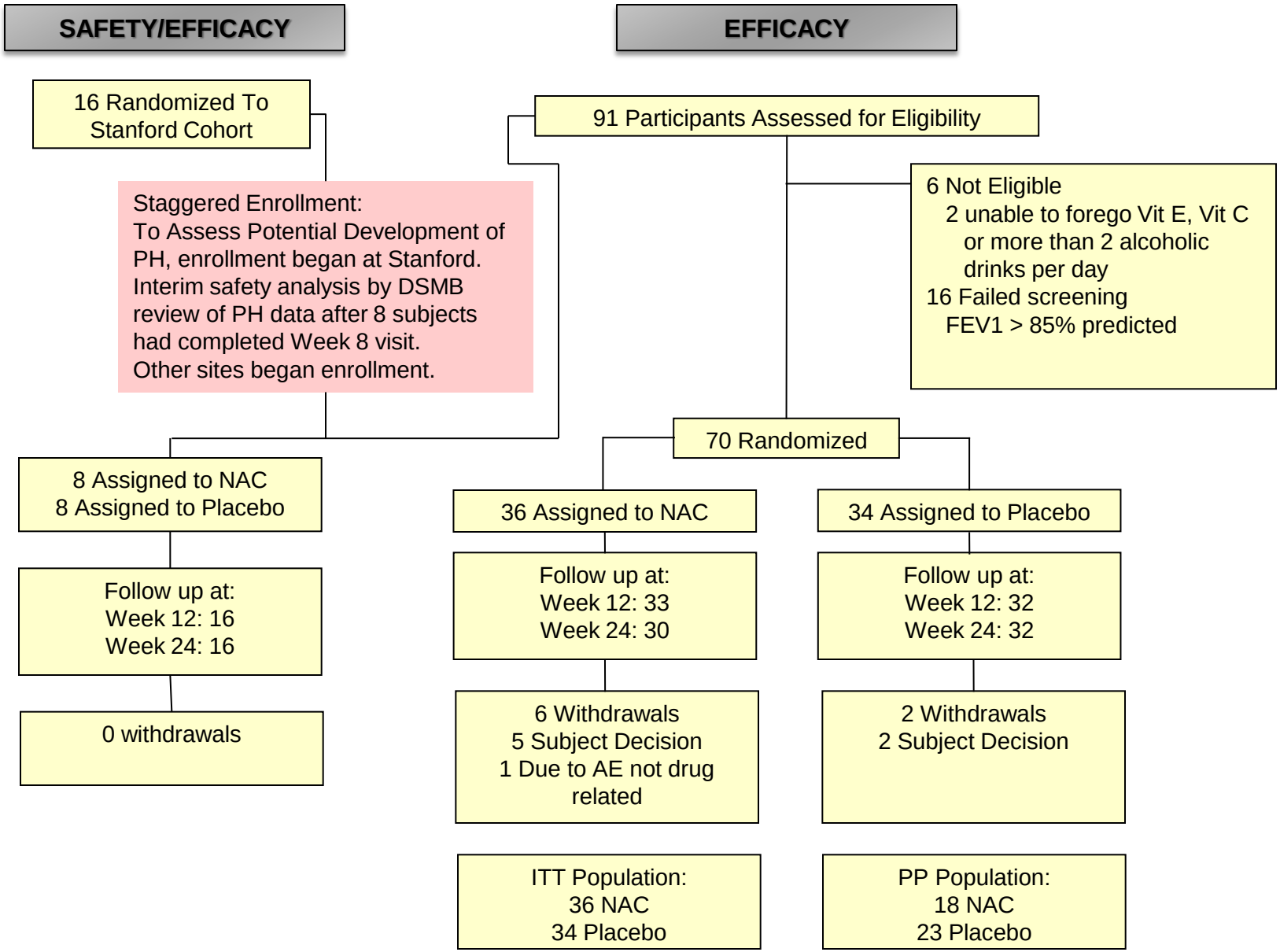
- Safety and tolerability
- Eval if NAC causes pulmonary hypertension if used chronically in high doses

Inclusion Criteria

- 7 years of age and older
  - Able to tolerate sputum induction
  - Perform reproducible spirometry
- Stable mild to moderate lung disease
- No use of acute antibiotics in prev. 4 weeks
- Must stop use of anti-oxidants in any form at least 6 weeks prior to and for the duration of the study
  - Usual doses of Vit E and C are allowed

Exclusion Criteria

- NSAID use in previous 1 week
  - To assure sputum neutrophil count and elastase are at 'baseline'
- Initiation of chronic dosing with azithro, ibuprofen, TOBI, IH Aztreonam or Colistin within previous 6 weeks
- Liver disease
- Active ABPA in previous 6 months
- Acetaminophen use in previous 3 days


SAFETY/EFFICACY
EFFICACY
16 Randomized To Stanford Cohort
Staggered Enrollment:
To Assess Potential Development of PH, enrollment began at Stanford.
Interim safety analysis by DSMB review of PH data after 8 subjects had completed Week 8 visit.
Other sites began enrollment.
8 Assigned to NAC
8 Assigned to Placebo
Follow up at:
Week 12: 16
Week 24: 16
0 withdrawals
91 Participants Assessed for Eligibility
6 Not Eligible
2 unable to forego Vit E, Vit C or more than 2 alcoholic drinks per day
16 Failed screening
FEV1 > 85% predicted
70 Randomized
36 Assigned to NAC
34 Assigned to Placebo
Follow up at:
Week 12: 33
Week 24: 30
Follow up at:
Week 12: 32
Week 24: 32
6 Withdrawals
5 Subject Decision
1 Due to AE not drug related
2 Withdrawals
2 Subject Decision
ITT Population:
36 NAC
34 Placebo
PP Population:
18 NAC
23 Placebo

Baseline Characteristics

	NAC (N=36)	Placebo (N=34)	Total (N=70)	P-value
	N (%)	N (%)	N (%)	
Female	16 (44)	19 (56)	35 (50)	0.34
DF508	18 (50)	16 (47)	34 (49)	0.46
7 - < 18 years	9 (25)	10 (29)	19 (27)	0.68
Azithromycin	23 (64)	24 (71)	47 (67)	0.55
AZLI or TOBI	23 (64)	17 (50)	40 (57)	0.24

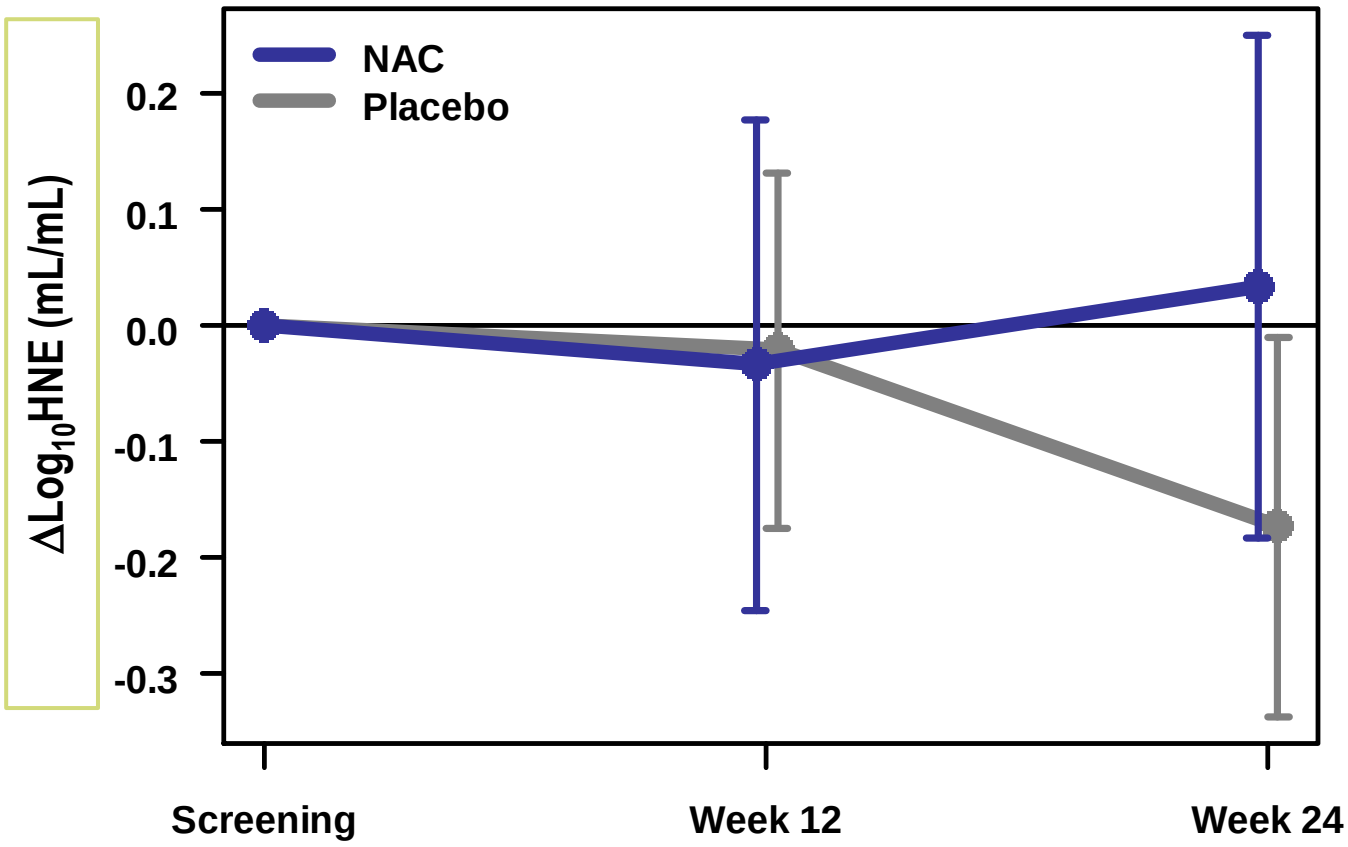
Baseline Characteristics – Pulmonary Function

	NAC (N=36)		Placebo (N=34)		Total (N=70)		P-value
FEV1 (% pred)	N	%	N	%	N	%	
40% - <60%	15	42%	13	38%	28	40%	0.77
60% - 85%	21	58%	21	62%	42	60%	
All x (SD)	62.9 (13.4)		63.8 (13.2)				0.44

Summary - Primary and Secondary Analyses

Variable	Treatment Effect (95% CI)	P-value
Sputum Neutr. Elastase (Log_{10})	0.21 (-0.07, 0.48)	0.14
Sputum Neutrophil Count (Log_{10})	2.6 (-12.1, 17.3)	0.73
Sputum IL-8 (Log10)	0.19 (-0.03, 0.42)	0.09
Plasma IL-8 (Log10)	-0.1 (-0.33, 0.14)	0.42
GSH in whole blood	64.2 (-177.6, 305.9)	0.60
FEV1 (% pred)	4.4 (0.83, 7.9)	0.02
FEV1 (L)	0.15 (0.03, 0.28)	0.02
Incidence of Pulm Exacerbation	-0.08 (-0.30, 0.14)	0.48
New use of antibiotics	0.08 (-0.14, 0.29)	0.50
CFQ-R Respiratory Domain	-0.34 (-6.3, 5.67)	0.91
CFRSD number of resp sx	-0.15 (-1.1, 0.8)	0.75

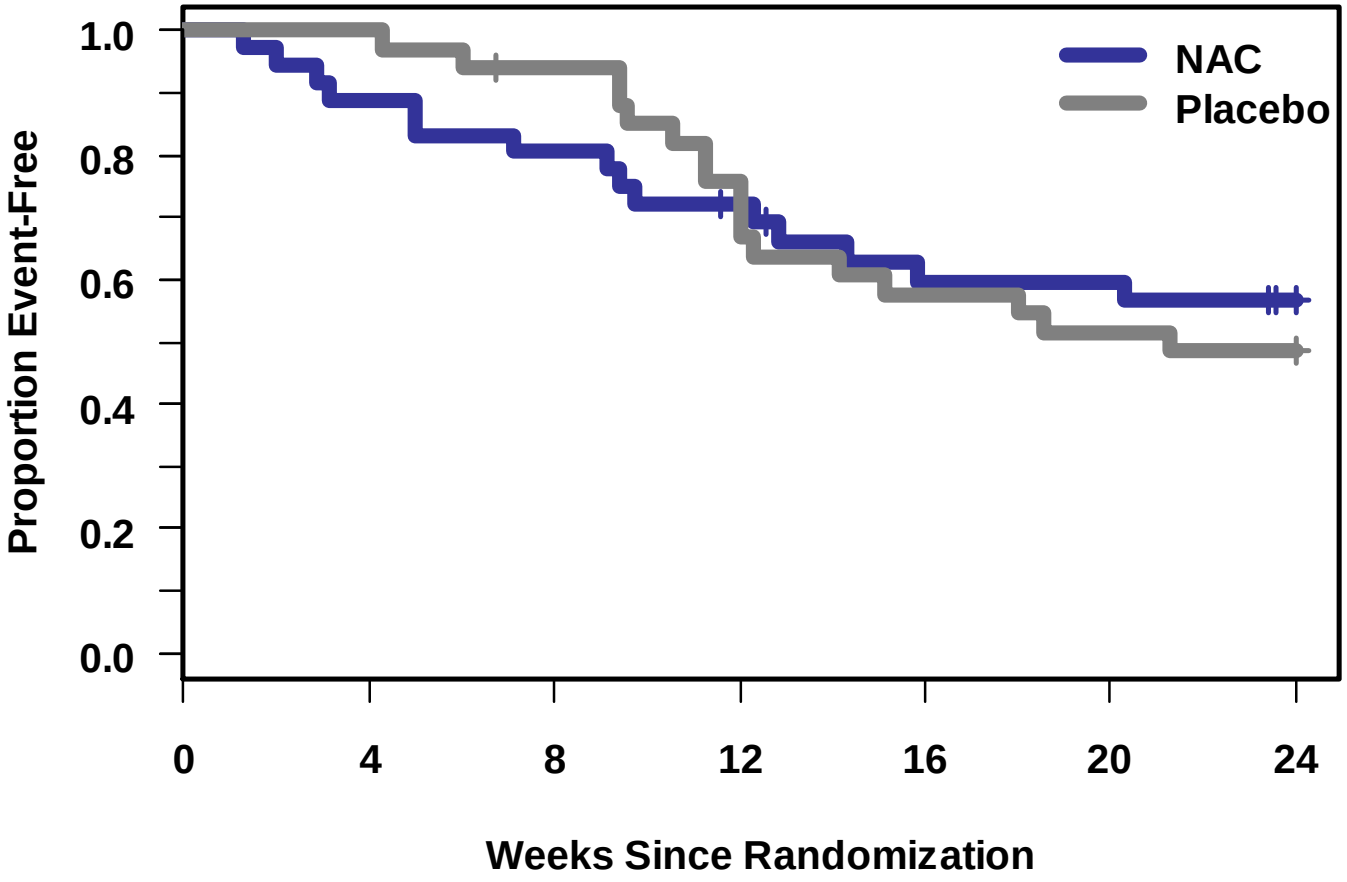
Neutrophil Elastase (Log_{10})



Exacerbations and Related Events

	NAC (N = 36)	Placebo (N = 34)	Difference (95% CI)	p-value
Pulmonary Exacerbation	15 (42%)	17 (50%)	-8% (-30%, 14%)	0.48
Sinus Exacerbation	10 (28%)	6 (18%)	10% (-10%, 29%)	0.31
Hospitalized	12 (33%)	12 (35%)	-2% (-23%, 19%)	0.86
Antibiotics	30 (83%)	28 (82%)	-2% (-23%, 19%)	0.86
Oral Antibiotics	22 (61%)	19 (56%)	5% (-17%, 27%)	0.66
Inhaled Antibiotics	26 (72%)	21 (62%)	10% (-11%, 31%)	0.35
IV Antibiotics	12 (33%)	12 (35%)	-2% (-23%, 19%)	0.86

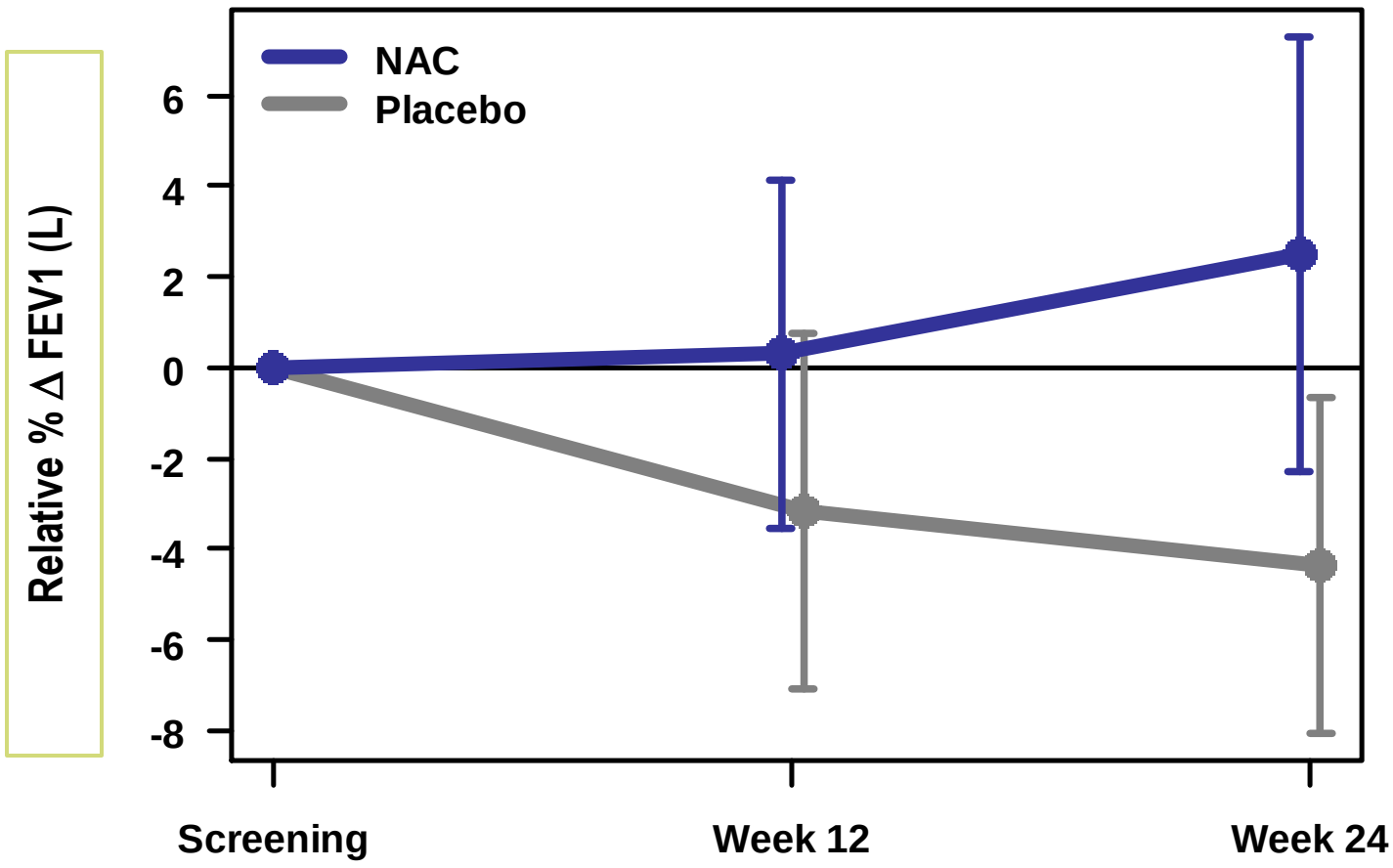
Time to Pulmonary Exacerbation



Adverse Events

	NAC (N=36)	Placebo (N=34)	Rate Ratio (95% CI)
Total number of AEs	357	349	
AE rate	0.43	0.43	1.00 (0.87, 1.16)
Avg. N. AEs per person	9.9	10.3	1.04 (1.22, 0.89)
Number (%) w/≥1 AE	33 (92%)	30 (88%)	
Total number of SAEs	26	29	
SAE rate	0.03	0.04	0.88 (0.52, 1.49)
Avg. N. SAEs per person	0.72	0.85	0.87 (1.69, 0.44)
Number (%) w/≥1 SAE	11 (31%)	12 (35%)	

Change in FEV1 (Absolute volume)



CFRSD Number of Respiratory Symptoms

		NAC (N=36)	Placebo (N=34)	Difference (95% CI)	p-value
Screening	N	35	31		
	Mean (SD)	2.69 (1.78)	2.29 (1.22)	0.4 (-0.36 1.15)	
Week 12 (Change)	N	32	29		
	Mean (SD)	0.00 (1.59)	0.34 (1.47)	-0.34 (-1.13 0.44)	0.38
Week 24 (Change)	N	30	29		
	Mean (SD)	0.43 (1.70)	0.59 (1.96)	-0.15 (-1.11 0.80)	0.75

CFQ-R Respiratory Score

		NAC (N=36)	Placebo (N=34)	Difference (95% CI)	p-value
Screening	N	36	34		
	Mean (SD)	70.76 (15.564)	72.06 (9.121)	-1.302(-7.43 4.83)	
Week 12 (Change)	N	31	31		
	Mean (SD)	0.09 (12.431)	-3.94 (11.670)	4.032(-2.09 10.16)	0.19
Week 24 (Change)	N	30	31		
	Mean (SD)	-4.82 (11.556)	-4.48 (11.865)	-0.336(-6.34 5.67)	0.91

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Discoveries and advances can't be made without your participation.
You are the best!