Phase IIa Clinical Trial Results with alidornase alfa for the Treatment of CF

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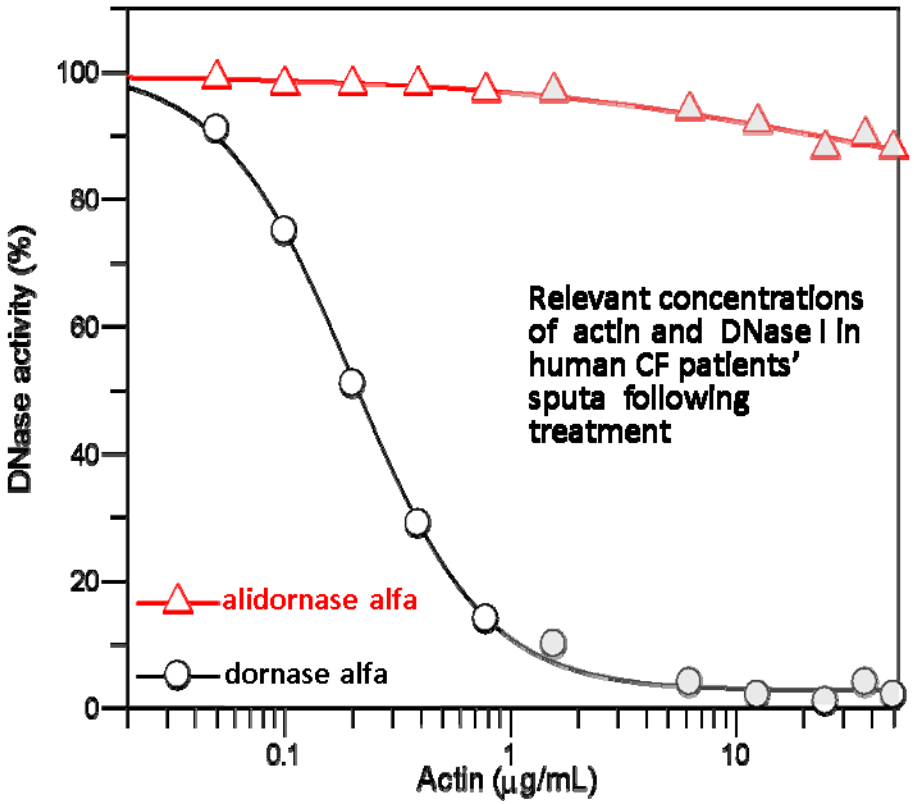
Alidornase alfa is designed for:

- Resistance to actin inhibition with improved kinetics
- Improved mucociliary clearance in CF
- Potentially improve lung function & reduce the risk of respiratory tract infections

Alidornase alfa compared to dornase alfa activity in the presence of actin concentrations corresponding to those found in CF patients' sputa



Phase IIa - Study Objective and Design

- **Objective:** Open Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Exploratory Efficacy Parameters of alidornase alfa in Patients with Cystic Fibrosis previously treated with dornase alfa

- Administration:
  Once daily inhalation of 2.5 mg alidornase alfa for 28 days

Main Inclusion Criteria:

- Age ≥ 12 years
- At least 4 months on dornase alfa & stable inhaled regimen
- Medically stable for at least one month prior to screening
- FEV1 of >40% and <90% ; FVC ≥ 40% at screening

Main Exclusion Criteria:

- History of lung transplantation
- History of adverse reactions during aerosol delivery
- History of hypersensitivity to inhaled proteins

Phase IIa –Study Population and Status

Demographics & baseline CF patient characteristics

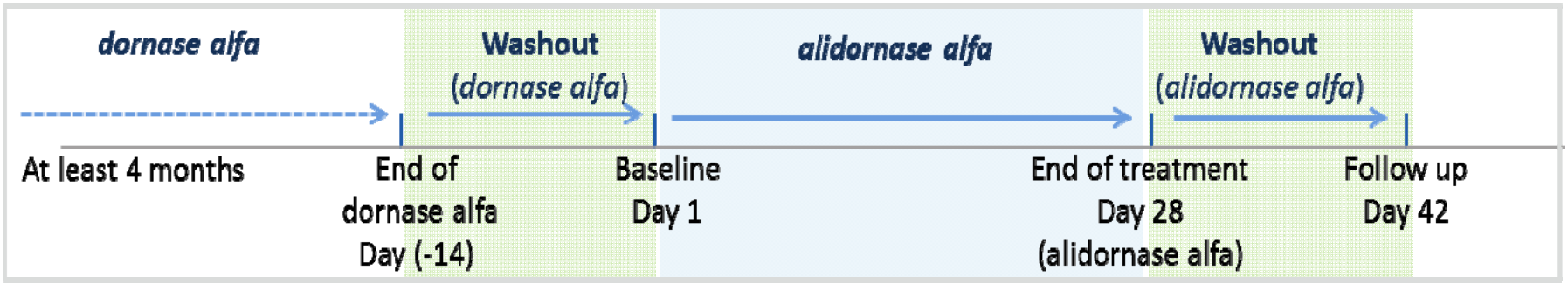
Total enrolled	16 CF patients
Age, yrs (Mean ± SD) (range)	25.8±9.1 (13-49)
Male : Female	10:6
Mean ppFEV1 ± SD (range) median ppFEV1	70.5% ± 10.8 (52-89) 70.5%
Pseudomonas aeruginosa , # positive subjects	8
Hypertonic saline, n (%)	4 (25%)

- All patients continued inhaled regimen of their respective CF medications throughout the study (steroids, hypertonic saline, antibiotics, etc.)
- All enrolled patients completed the 28 day treatment period

Phase IIa – Study Endpoints and Overall Design

- Safety and immunogenicity
- Pharmacokinetics
- Exploratory efficacy:
  - Effects on FEV1
  - Effect on sputum DNA parameters
  - Effect on rheology parameters

Study Design:



Phase IIa – Safety

100% (24 AEs)* Total AEs in 11/16 subjects		
AEs mild and moderate	96% (23)	
Severe AEs	4% (1)	Severe AE was not treatment related (anemia)
Serious AEs	0% (0)	
Related, possibly related	33% (8)	Vomiting, Throat irritation, Cough, Diarrhea, Dysphonia, Nausea
Not related, unlikely related	67% (16)	Anemia, Gastrointestinal haemorrhage, Infective pulmonary exacerbation, Upper respiratory tract infection, Viral upper respiratory tract infection, Hypokalaemia, Myalgia, Cough, Dyspnoea, Haemoptysis, Rales, Sputum increased

* **as reported by Investigators**

Phase IIa – Pharmacokinetics & Immunogenicity

- **Plasma Pharmacokinetics (PK)**

alidornase alfa was found not to be absorbed to the circulation as part of GLP PK study using ELISA

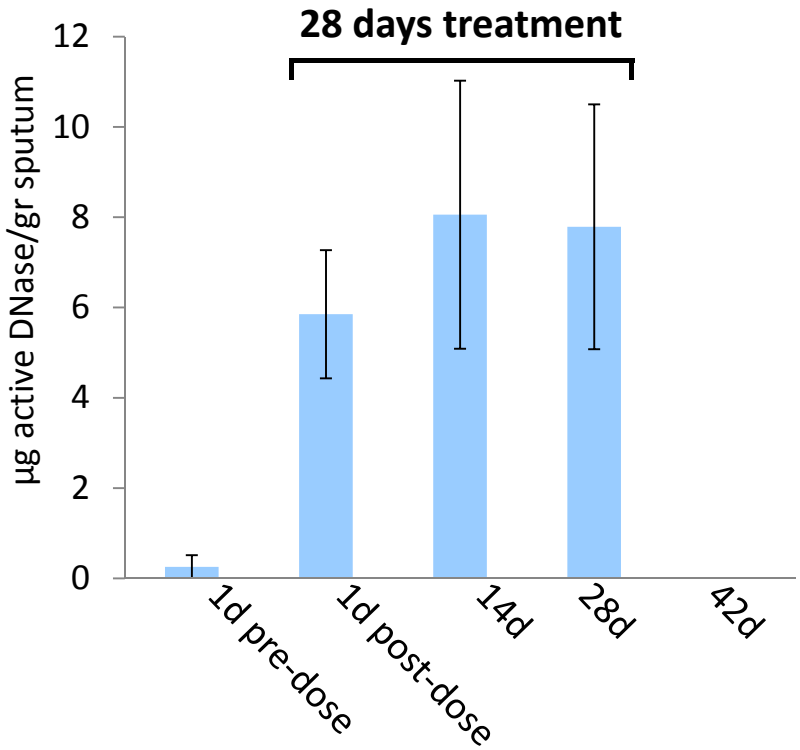
- **Activity in Sputum**

Active alidornase alfa was detected in the patients' sputa during the entire treatment period

- **Immunogenicity**

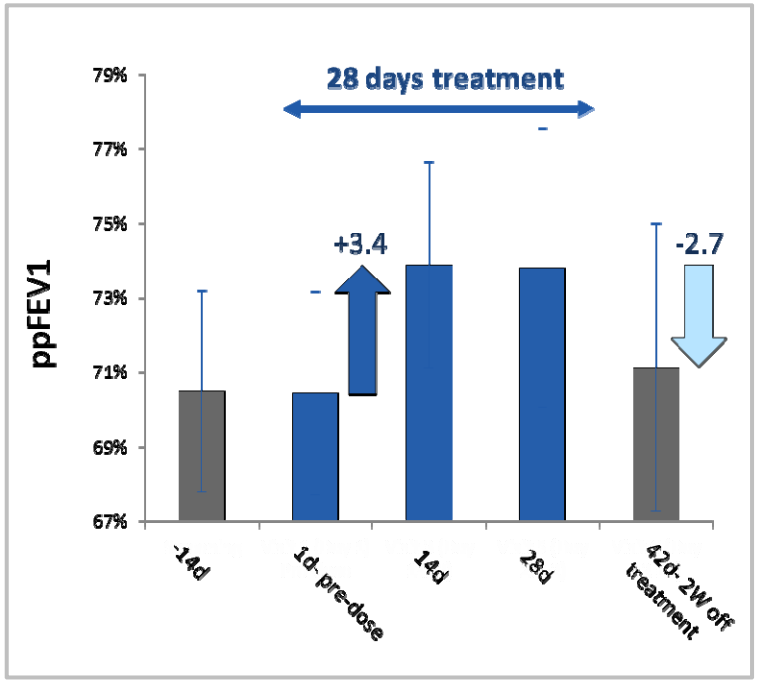
Only 1 /16 patients was found to be treatment induced positive for anti-alidornase alfa (maximal low titer of 298 at visit 5)

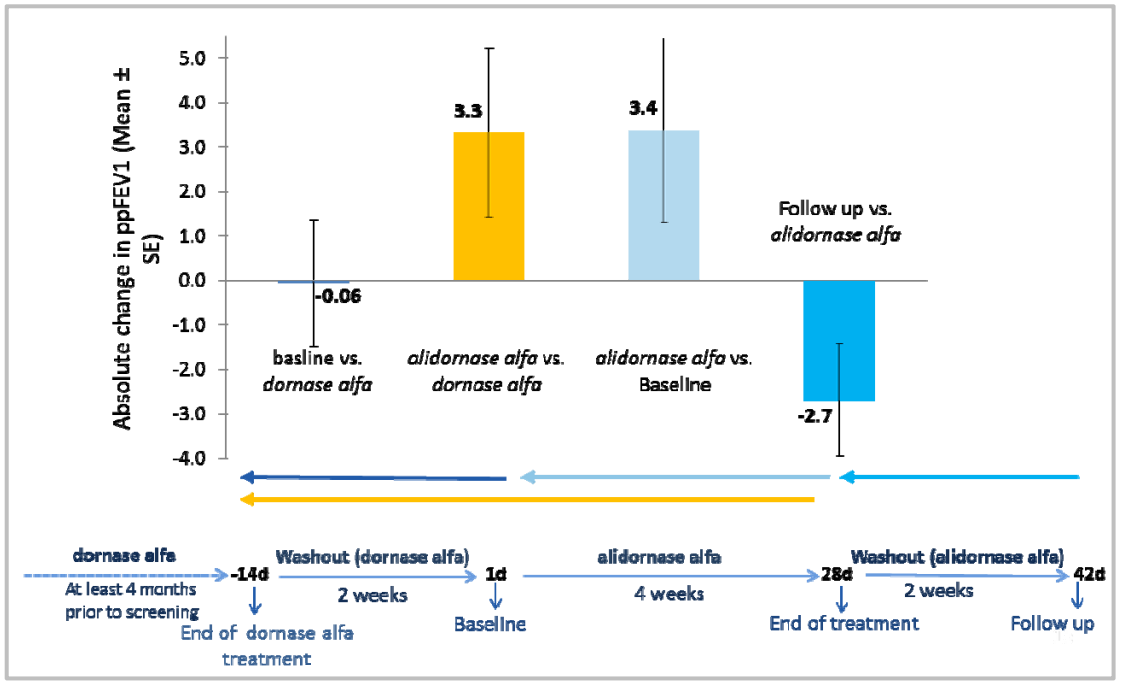
alidornase alfa activity in Sputa*



* By Methyl green-based enzymatic activity assay

alidornase alfa Effect on Lung Function

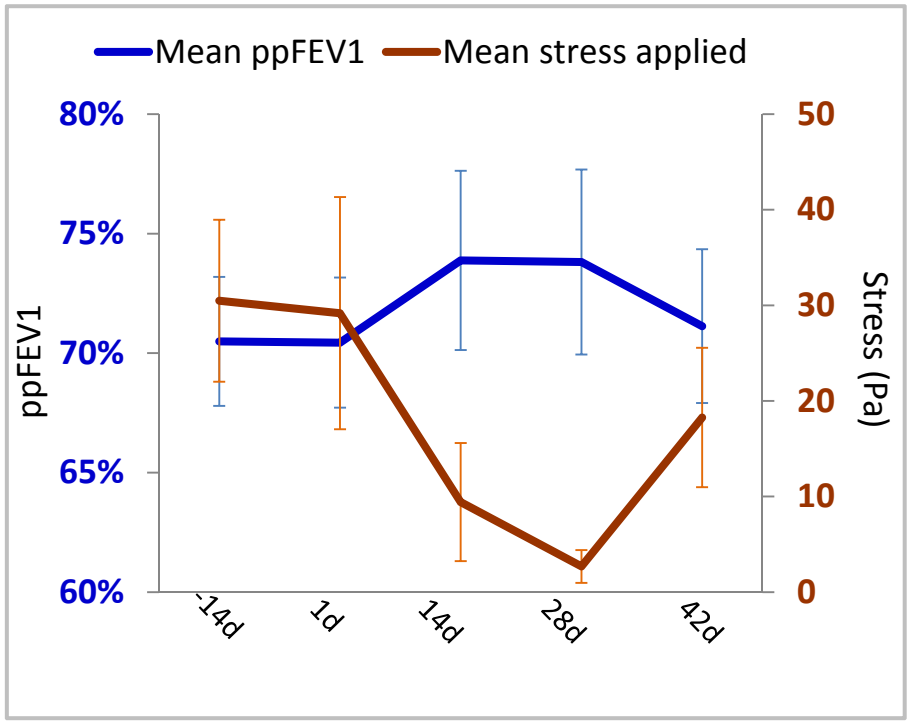




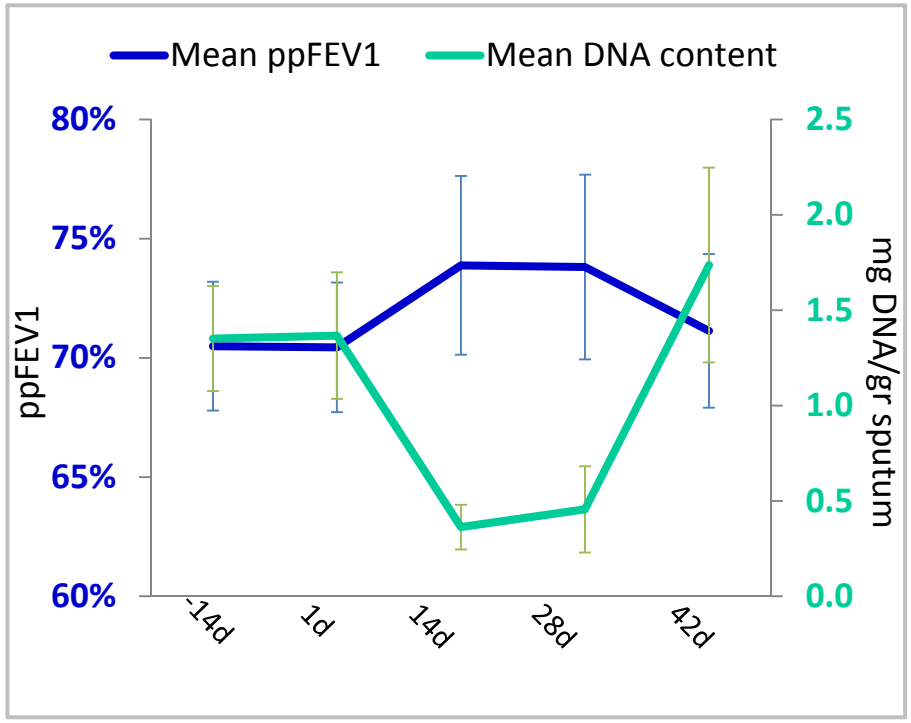
- No change in ppFEV1 was observed during the washout period from dornase alfa
- Following 4 weeks of daily treatment with alidornase alfa, improvement in mean absolute ppFEV1 was rapid and sustained
- The observed improvement shown with alidornase alfa was lost within 2 weeks of therapy discontinuation, causing a reduction in ppFEV1

ppFEV1 Correlation with DNA Content and Sputa Viscoelasticity

Sputum viscoelasticity vs ppFEV1



DNA content in sputum vs ppFEV1



Improvement in ppFEV1 following treatment with alidornase alfa correlates with:

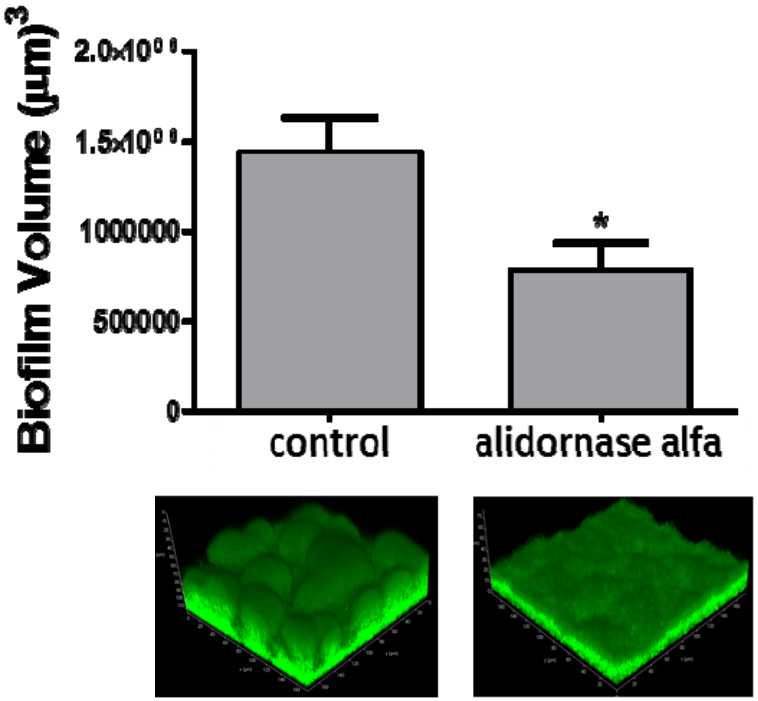
- mean reduction of ~70 % in DNA content from baseline
- mean reduction of > 90% in sputa viscoelasticity from baseline

Alidornase alfa Potential in Lowering *P. aeruginosa* Respiratory Infections

Evaluation of Phase IIa patients sputa for *P. aeruginosa* presence:

Method	Patients (total: 9 tested)	Results before and after alidornase treatemnt	
		Baseline	End of treatment
qPCR	4	Negative	Negative
	5	Highly positive	> 70% reduction
Positive Patient #	**per Medical history**	**Baseline**	**End of treatment (% decrease)**
03-01	Chronic colonization	Positive	Positive (93%)
03-03	Chronic colonization	Positive	Negative (100%)
03-04	Chronic colonization	Positive	Negative (100%)
04-01	Chronic colonization	Positive	Positive (77%)
05-01	Chronic colonization	Positive	Negative (100%)

Ex vivo: Biofilm Inhibition of *Pseudomonas aeruginosa* PAO1



Reduction of over 70% in the presence of *Pseudomonas aeruginosa* (qPCR) as a result of alidornase alfa treatment, reinforced by ex vivo observations

Phase IIa: Conclusions

alidornase alfa - human rDNase I, Resistant to actin inhibition

Safety:

alidornase alfa was safe & well tolerated

- Low incidence of treatment related/possibly related AEs
- All AEs were resolved without sequelae
- No SAE
- Low incidence of treatment induced Anti Drug Antibodies

Pharmacokinetics:

- Alidornase alfa was not absorbed to the circulation
- Active alidornase alfa was measured in patient's sputa

Efficacy: alidornase alfa improved lung function:

- Mean absolute increase in ppFEV1 of 3.4 points from baseline
- Mean absolute increase in ppFEV1 of 3.3 points over dornase alfa
- Mean absolute decrease in ppFEV1 of -2.7 points following alidornase alfa 2 weeks washout period
- Sputa analyses form available samples indicates:
  - A mean reduction of ~70 % in DNA content from baseline
  - A mean reduction of > 90% in sputa viscoelasticity from baseline
  - Reduction of over 70% in the presence of pseudomonas (qPCR)

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Lea Bentur	Rambam Medical Center, Haifa, Israel

- **Study site clinical teams and co-authors**

Thank You