C-1

Dry Powder Mannitol (DPM)

Pharmaxis
Pulmonary and Allergy Drugs Advisory Committee
January 30, 2013

C-2

Dry Powder Mannitol (DPM)

Ronald L. Dundore, PhD
Vice President, US Regulatory Affairs
Pharmaxis

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Proposed Indication

DPM is indicated for the management of cystic fibrosis in patients aged 6 years and older to improve pulmonary function.

Limitation of Use

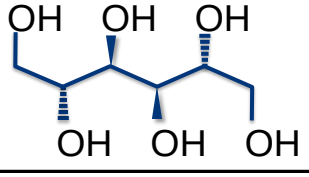
DPM has not been studied in patients with an FEV_1 < 30% predicted, or in patients with a history of recent significant hemoptysis.

Benefit-risk in patients with FEV_1 < 40% not clearly established.

C-4

Proprietary Formulation of Mannitol

- Generally Recognized as Safe (GRAS)
- DPM for cystic fibrosis (CF)
  - 400mg BID
  - Approved in EU and Australia
- Aridol®, test for bronchial hyperresponsiveness
  - 635mg of inhaled mannitol



C-5

Mannitol: Shown to Improve Airway Clearance

- Nonclinical studies of mannitol
  - Influx of water into airway
  - Increases airway surface liquid
  - Increases transportability of mucus
  - Increases ciliary beat frequency

C-6

Mannitol: Shown to Improve Airway Clearance

- In clinical studies mannitol improves mucociliary clearance in patients
- Hydrates the lung surface leading to improved airway clearance

C-7

DPM:
Engineered for Optimal Deposition

- 3 µm spheres maximizes lung deposition
- 40mg/capsule - 400mg total dose
- Breath-actuated dry powder inhaler

C-8

Using the DPM Inhaler

C-9

DPM: Therapy Time ~ 5 minutes

- 400mg dose administered ~ 5 minutes
- Portable
- Disposable = no cleaning
- Designed for patient convenience

C-10

Agenda

Unmet Medical Need	**Felix Ratjen, MD, PhD, FRCPC** Professor, Pediatric Respiratory Medicine University of Toronto Hospital for Sick Children
Efficacy	**Howard Fox, MD** Chief Medical Officer Pharmaxis
Safety	**Brett Charlton, MD, PhD** Medical Director Pharmaxis
Risk/Benefit and Clinical Perspective	**Patrick Flume, MD** Professor, Pulmonary and Critical Care Medicine Medical University of South Carolina

C-11

Additional Experts

Diana Bilton, MD	Consultant and Honorary Senior Lecturer Royal Brompton Hospital, London
Simon Day, PhD	Independent Statistical Consultant

C-12

Disease Background and Unmet Medical Need

Felix Ratjen, MD, PhD
Hospital for Sick Children
University of Toronto

C-13

CF is a Life Shortening Genetic Disease[1]

- Autosomal recessive genetic disease
- ~30,000 diagnosed patients in the US
  - 90% caucasians
- 1,000 new cases diagnosed each year
- Most patients are diagnosed shortly after birth
- Estimated life expectancy of 38 years
  - Incremental improvement to outcomes

[1] Cystic Fibrosis Foundation Patient Registry, 2010 Annual Data Report, Bethesda, Maryland© 2011.

C-14

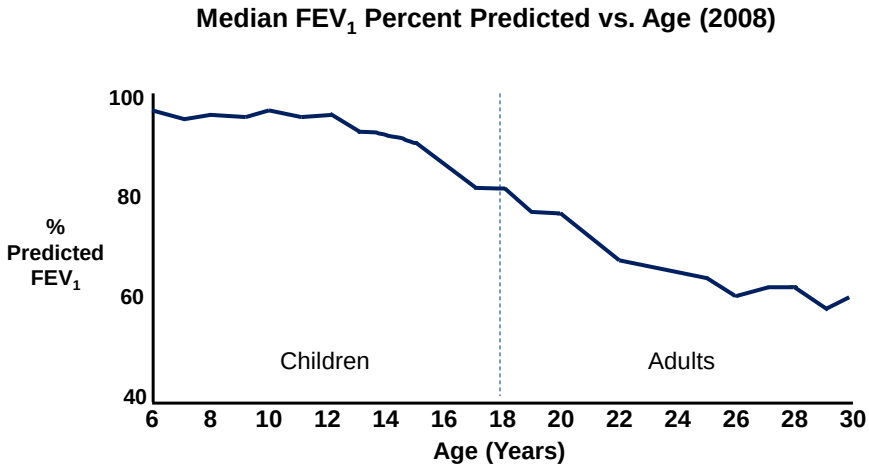
CF Disease Focuses on the Airways[1]

- Multi-organ disease
- 75% of all hospitalizations caused by pulmonary morbidity
- 90% of premature deaths from respiratory system effects

[1]Orenstein, DM., Cystic Fibrosis: A Guide for Patient and Family.

C-15

Lung Disease is Progressive in CF and Lung Function Declines Over Time



CFF Patient Registry, 2009 Annual Data Report Bethesda, Maryland © 2011 Cystic Fibrosis Foundation

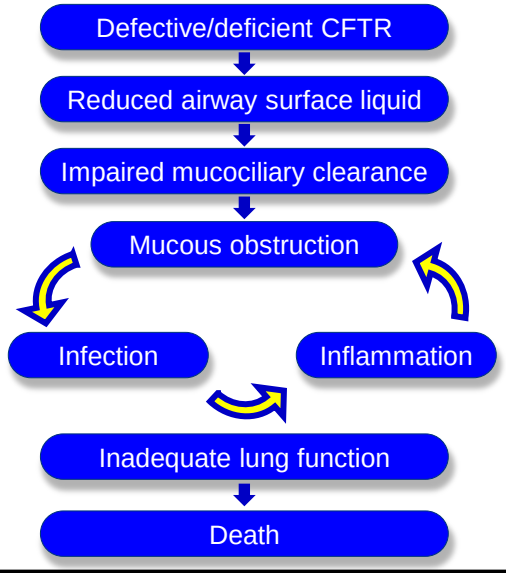
C-16

CF Therapy Goal is to Delay Decline in Lung Function

- Exacerbations and infections lead to lung function decline
  - Incidence increases with disease progression
- Seek to lessen exacerbations

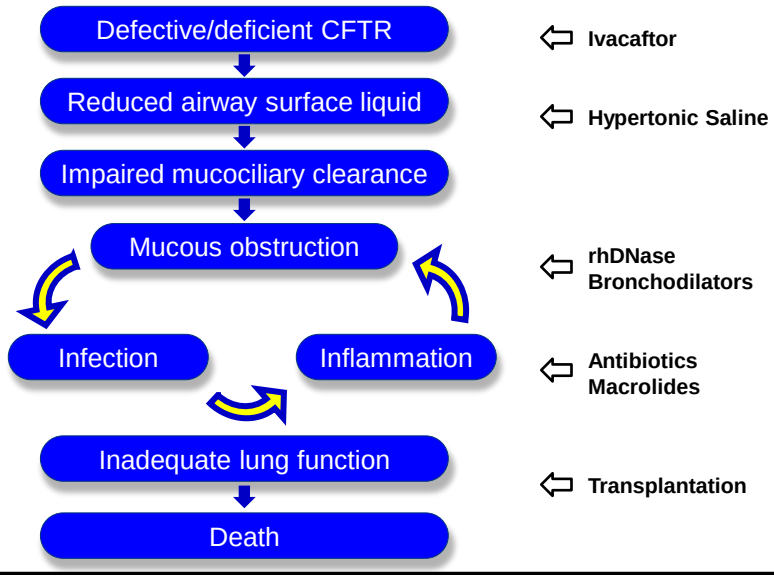
C-17

CF Pathophysiology



C-18

Therapies Recommended in CF Guidelines



C-19

Not Every CF Patient Will be Treated with All Recommended Products

- Try to treat with each product
- Individualize treatment based on response, tolerability and acceptability by patients

C-20

Challenges of Nebulized Therapy

- Treatment burden high
  - Average 7 therapies per day[1]
  - Around 2 hours per day[2]

[1] Sawicki GS et al., Journal of Cystic Fibrosis 8, 2009; [2]Sawicki GS, et al., J Cyst Fibrosis., 2009.

C-21

Challenges of Nebulized Therapy

- Requires setup and cleaning[1]
- Only 1/3 of patients follow recommended cleaning procedures[2]
- Bacterial contamination of nebulizers is common (65% in one study[3])

[1]Sawicki GS et al., Journal of Cystic Fibrosis, 8 (91-96), 2009.; [2]Melani S, et al., Eur Respir J., 2001.; [3]Blau H, et al. Child Care Health Dev., 2007.

C-22

Need Options that Can be Added to CF Therapy to Improve Lung Health

- Improve airway clearance by enhancing mucociliary clearance (MCC)
- Any incremental FEV_1 improvements regarded as clinically meaningful
- Reduce exacerbations are equally important
- Limit additional burden of treatment
  - Improve compliance & persistency

C-23

Efficacy

Howard Fox, MD
Chief Medical Officer
Pharmaxis

C-24

Efficacy Overview

- Clinical program overview
- Phase 3 design and efficacy results
  - CF-301 and CF-302
- Subgroup analyses - pooled data

C-25

Key Analysis Issues

- CF-301 - impact of missing data on interpretation of primary endpoint
  - Sensitivity analyses
- CF-302 - primary endpoint p=0.059

C-26

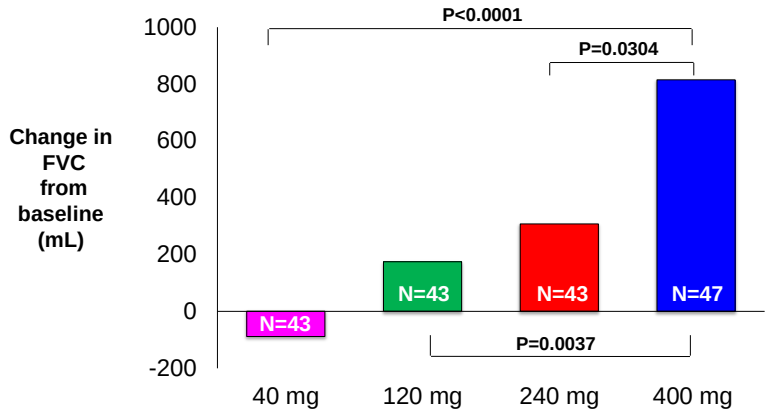
Clinical Development Program

Phase 2	Phase 3 Randomized, Double Blind
CF-201 Efficacy & Safety n=39 420mg bid vs. placebo	CF-301 Efficacy & Safety ITT n=295 400mg bid vs. 50mg BID Control
CF-202 Dose Response n=48 40, 120, 240, 400mg BID	CF-302 Efficacy & Safety ITT n=305 400mg bid vs. 50mg BID Control
CF-203 Efficacy & Safety n=26 400mg BID vs 2.5mg rhDNase vs. Combo	

C-27

CF-202: Mannitol 400mg B.I.D. is Most Effective Dose Evaluated

Effect of different dosage regimens on FVC (mL) after 2-week treatment in patients with CF



Teper et al. 2011 J Cyst Fibr:10;1-8

C-28

Clinical Trials with 93 Sites Worldwide

CF-301 sites

- UK: 24
- Australia: 10
- Ireland: 4
- New Zealand: 2

CF-302 sites

- USA: 28, 139 patients
- Argentina: 8
- France: 6
- Belgium: 4
- Canada: 3
- Germany: 3
- Netherlands: 1

C-29

CF-301 and CF-302: Study Design

- Multi-center
- Randomized
- Double blind, controlled
- 6 month safety and efficacy studies
- 3:2 randomization (DPM:control)

C-30

CF-301 and CF-302: Study Design

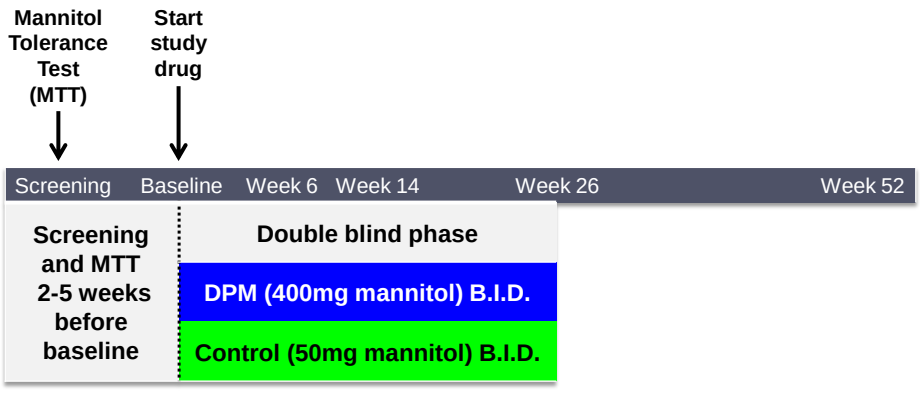
- Confirmed diagnosis of cystic fibrosis
- ≥ 6 years of age
- FEV_1 ≥ 30% (40% CF-302) and < 90 % predicted
- All standard CF therapies allowed except hypertonic saline
- Passed Mannitol Tolerance Test (MTT)
- Routine pre-dose bronchodilator

C-31

CF-301 and CF-302: Study Design

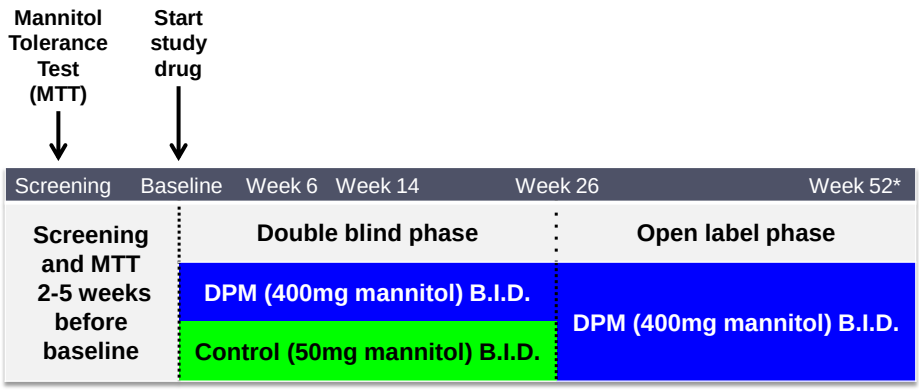
C-32

CF-301 and CF-302: Study Design



C-33

CF-301 and CF-302: Study Design



* In a few selected centres in CF-301 the open label phase extended up to 78 weeks

C-34

CF-301: Efficacy Results

C-35

CF-301: Efficacy Endpoints

- Primary
  - Change from baseline in FEV_1 over 26 weeks
- Secondary endpoints included
  - Other lung function parameters
  - Pulmonary exacerbations (Fuchs' criteria)
  - Sputum weight
- Endpoints analyzed based on rhDNase use

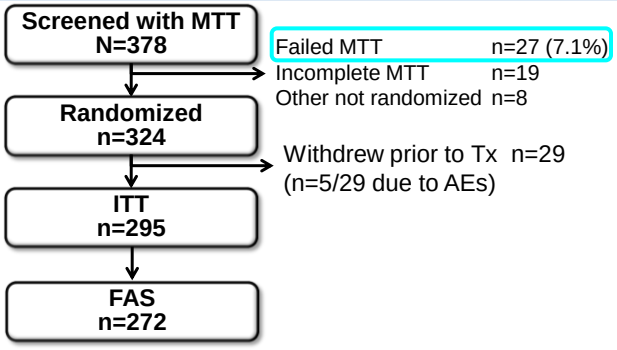
C-36

CF-301: Statistical Methodology

- Primary analysis model
  - Mixed model repeated measures (MMRM)
  - Requires at least one follow up measure
  - Population: full analysis set (FAS)
- ITT population used in other analyses including sensitivity of primary endpoint

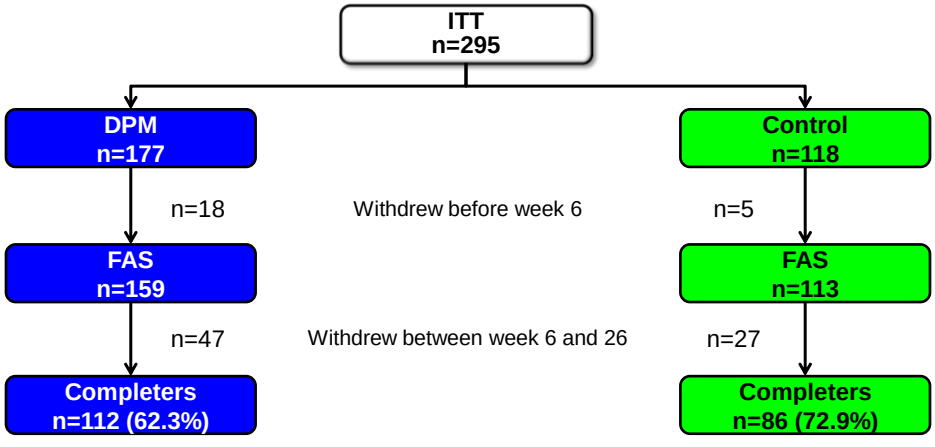
C-37

CF-301: Subject Disposition



C-38

CF-301: Subject Disposition



C-39

CF-301: Reasons for Withdrawal

	DPM N=177 (%)	Control N=118 (%)
Subject withdrew consent	15.8	18.6
Adverse event	16.4	9.3
Physician decision	3.4	0
Sponsor decision	0.6	0
Other	0.6	0
Withdrawals total	36.7	28.0

ITT population

C-40

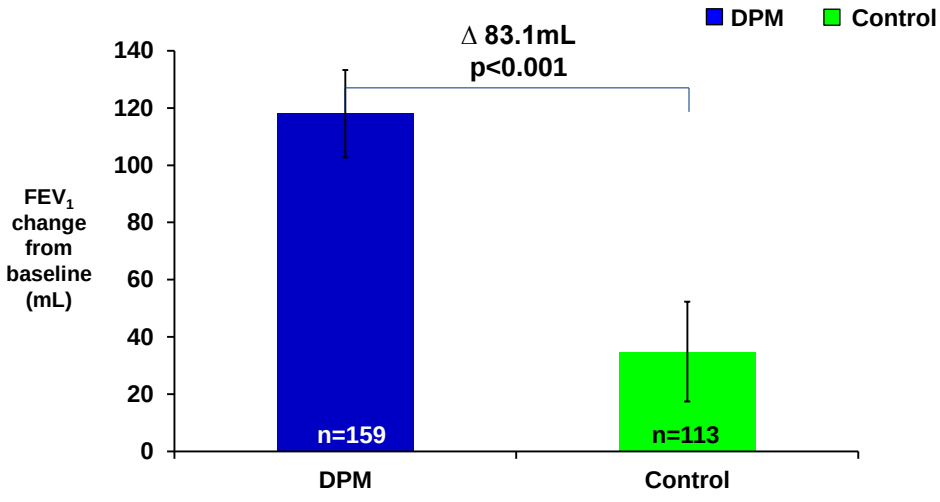
CF-301: Demographics

Variable at Baseline (ITT population)	CF-301 N=295	
	DPM N=177	Control N=118
Mean age years (SD)	23.1 (11.7)	22.8 (10.8)
Gender (female)	40.1%	51.7%
FEV_1 % predicted (SD)	62.4 (16.5)	61.4 (16.1)
FEV_1 volume (L) (SD)	2.1 (0.8)	2.0 (0.7)
Regular medication		
rhDNase	54.2%	56.8%
Inhaled/Nebulized Antibiotics	55.4%	61.0%

C-41

CF-301: Primary Endpoint Results Significant Improvement in Lung Function

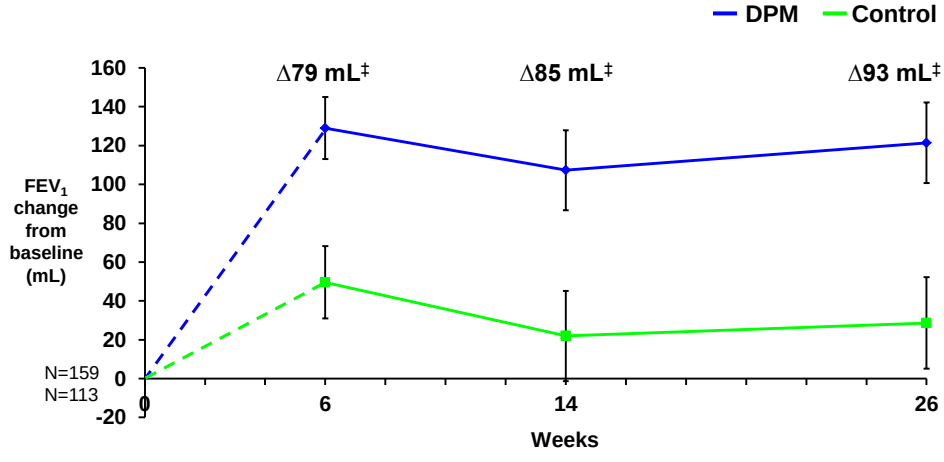
Overall Effect Size (FEV_1) Over 26-weeks – FAS Population



Error Bars represents ±SEM; Model = MMRM

C-42

CF-301: Change in FEV_1 Over Time



Post-hoc analysis; FAS population; ‡p<0.05; Error Bars represents ±SEM; Model = MMRM

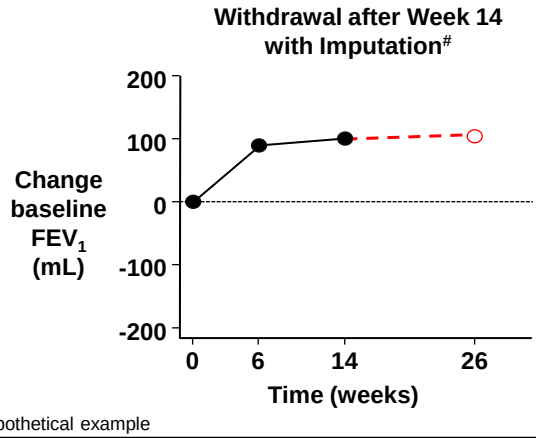
C-43

Evaluating Impact of Missing Data

C-44

CF-301 Withdrawals: Possible Bias Using MMRM

- MMRM assumes missing data are missing at random

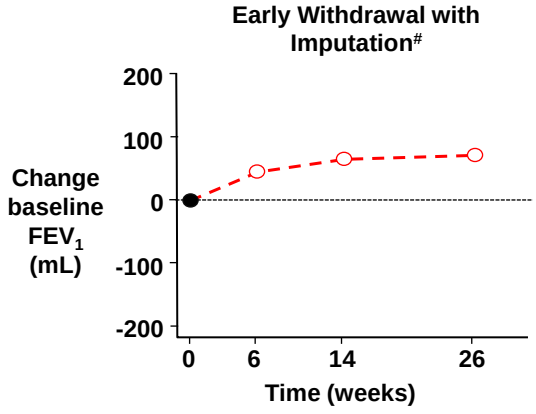


Not real data – hypothetical example

C-45

CF-301: Withdrawals before Week 6 have No Data to Inform MMRM Imputation

- Early withdrawal: prior to week 6
  - No post-baseline FEV_1 data, prevents informed estimation of FEV_1 changes



Not real data – hypothetical example

C-46

CF-301: Withdrawals before Week 6

	DPM N=177 (%)	Control N=118 (%)
Withdrew consent	4.5	4.2
Adverse event	5.1	0
Physician decision	0.6	0
Total	10.2	4.2

ITT population

C-47

CF-301: Withdrawals

- 272/295 (92%) of the ITT population contribute to primary analysis

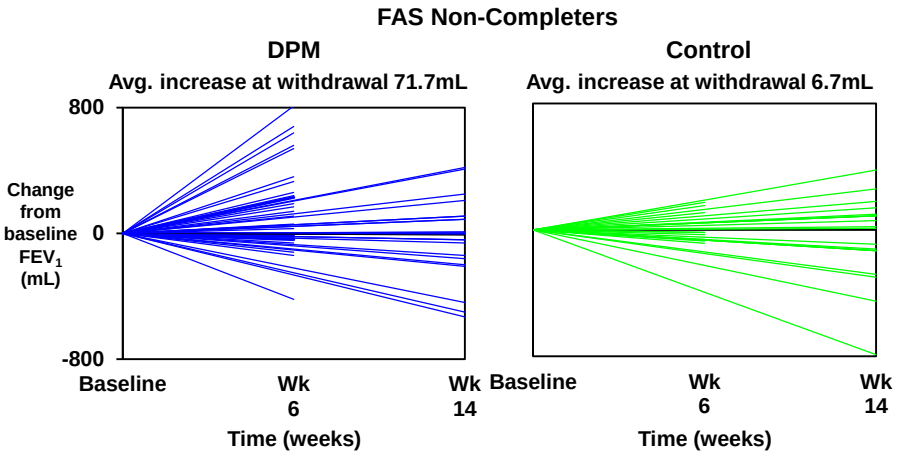
C-48

CF-301: Withdrawal after Week 6

- Withdrawal after week 6 onwards comparable between groups
- Data is available to inform the imputation

C-49

CF-301: FEV_1 Change from Baseline at Time of Withdrawal after Week 6



C-50

CF-301: Sensitivity Analyses Rationale

- Evaluate primary endpoint using ITT
- Account for differential drop-out missing data
- NRC expert report[1] on treatment of missing data in clinical trials
  - No universal method for handling missing data
  - Favored multiple-imputation models
  - Pattern mixture models recommended to assess robustness
  - Robust if the treatment effect maintained despite clinically plausible penalties

[1]N Engl J Med 2012.

C-51

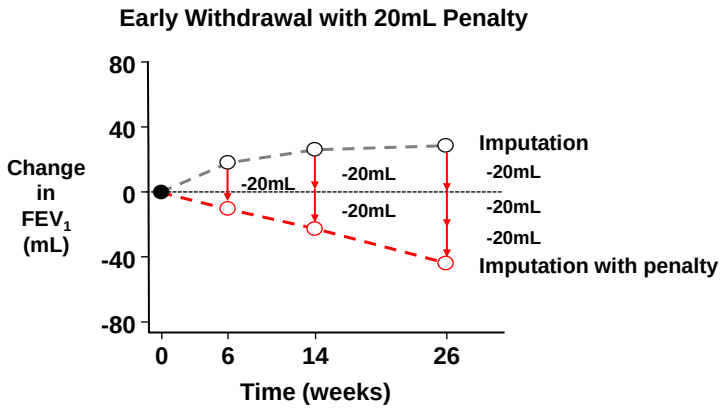
CF-301: Sensitivity Analyses Consistent with NRC Recommendations

- MMRM using ITT
  - Multiple imputation (MI)
  - Pattern mixture model (MI with 20mL penalty)*

*Post hoc; Ref: Little et al, N Engl J Med 2012.

C-52

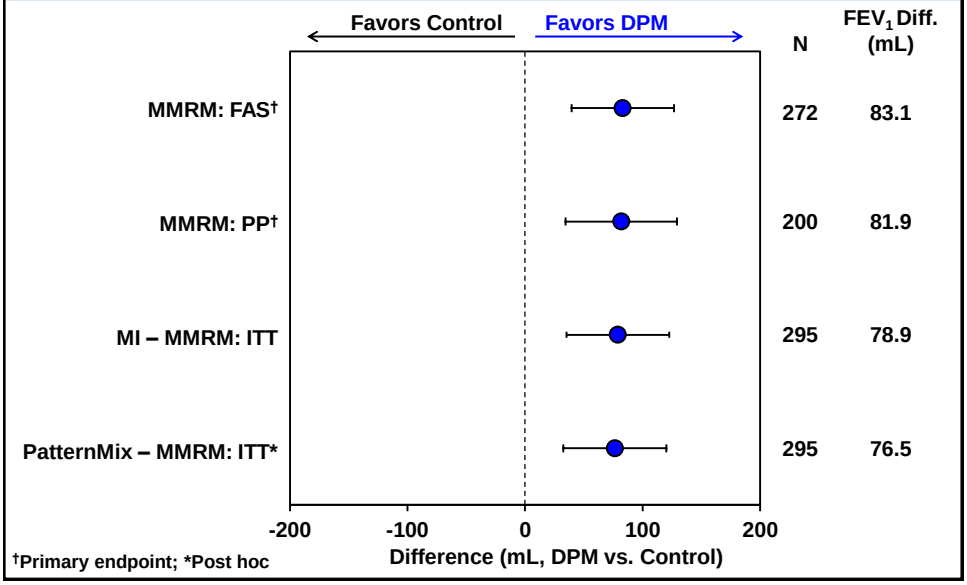
Pattern Mixture Model: Multiple Imputation with Penalty for Missing Data



Not real data – hypothetical example

C-53

CF-301: Sensitivity Analyses for FEV_1



†Primary endpoint; *Post hoc

C-54

Evaluation of Robustness Through Use of a Tipping Point

- Tipping point – size of penalty needed to prevent a significant effect in ITT using a pattern mixture model

C-55

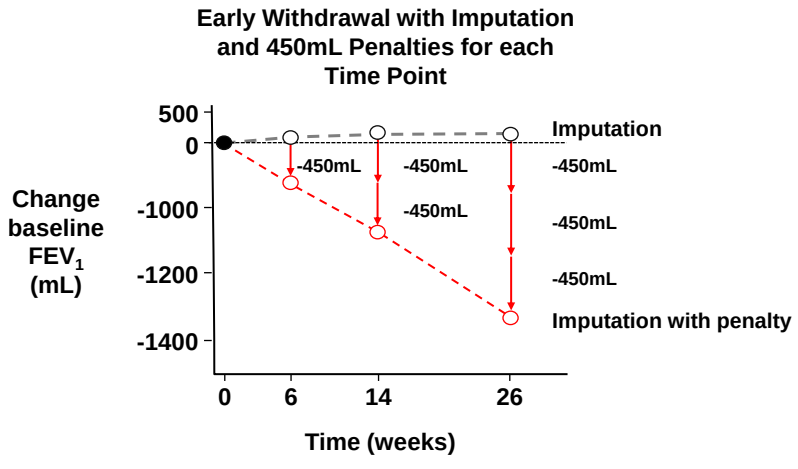
CF-301: Pattern Mixture Model Tipping Point Results (Scenario 1)

	Pattern Mixture - MMRM	
Penalty per missing visit	Tx effect	p-value
100 mL	67.5	0.0034
250 mL	58.5	0.0195
400 mL	55.5	0.0419
450 mL	55.1	0.0499
500 mL	54.7	0.0583

- All patients withdrawing before week 6 are penalized by 1350mL

C-56

Pattern Mixture Model: Tipping Point Penalty 1350 mL with Early Withdrawal



Not real data – Hypothetical Example

C-57

CF-301: Pattern Mixture Model Tipping Point Results (Scenario 2)

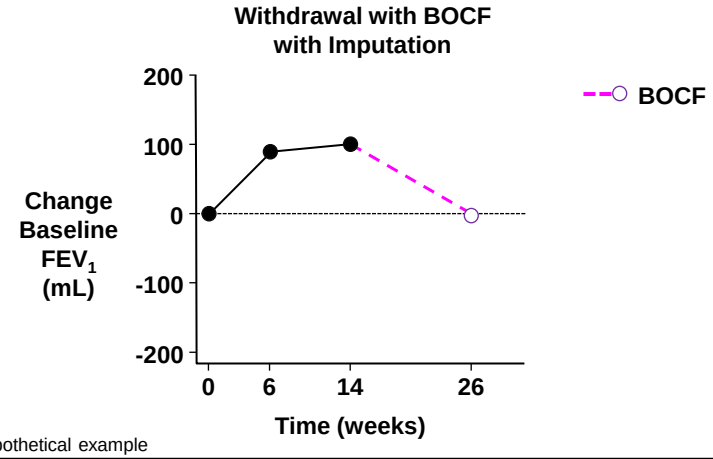
		Pattern Mixture - MMRM	
DPM penalty per missing visit	Control penalty per missing visit	Tx effect	p-value
20 mL	0mL	73.4	0.0010
50 mL	0mL	65.5	0.0037
100 mL	0mL	54.1	0.0182
150 mL	0mL	45.6	0.0511

- DPM patients withdrawing before week 6 are penalized by 450mL
- Control patients withdrawing before week 6 are penalized by 0mL

C-58

CF-301: Sensitivity Analyses Consistent with NRC Recommendations

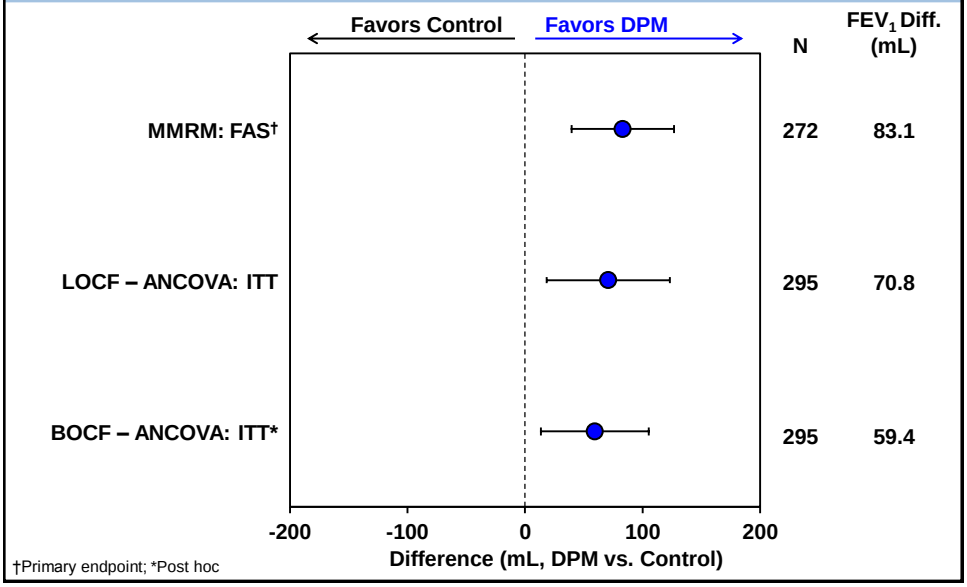
ANCOVA at week 26 using ITT
BOCF = baseline observation carried forward



Not real data – hypothetical example

C-59

CF-301: Sensitivity Analyses for FEV_1



†Primary endpoint; *Post hoc

C-60

Limitations of Using a Dichotomous Approach

- A dichotomous responder approach assumes a value above or below which there is an effect
- Large loss of power using dichotomous rather than continuous variable
  - 71% power using ANCOVA BOCF at week 26 (59.4mL) vs. 24% power using 100mL response
- Using all data available in the ITT population at each time point is more informative than thresholds at one time point

C-61

CF-301: Responder Thresholds Applied to ITT and Completers

Responder thresholds	ITT (per FDA) DPM N=176 Control N=118	Completers DPM N=111 Control N=86
FEV_1 absolute increase in mL	Odds ratio (95% CI)	
≥50*	1.23 (0.75, 2.02)	2.41 (1.29, 4.52)
≥75*	1.34 (0.80, 2.24)	2.37 (1.29, 4.36)
≥100	1.31 (0.78, 2.21)	1.97 (1.08, 3.58)

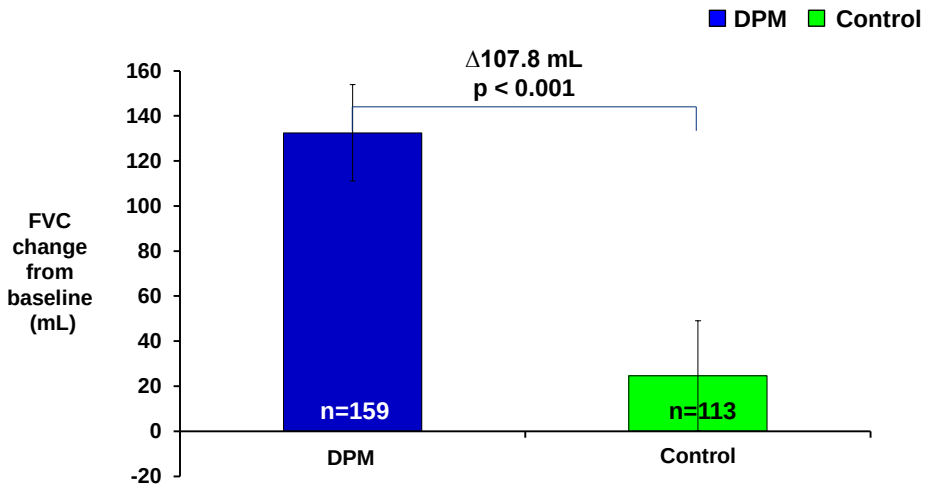
*Post-hoc

C-62

CF-301: Secondary Endpoints

C-63

CF-301: Improvements in FVC Consistent with Improved Airway Clearance



FAS population; Error bars represents ±SEM; Model = MMRM

C-64

CF-301: Exacerbations Key to CF Management

- Exacerbations associated with pulmonary function decline[1,2,3] and increased mortality[4,5,6]
- Clinically important but challenging variable due to infrequency
- Individual study size would be impractical

[1]Amadori et al Respir Med 2009; [2]Waters et al ERJ 2011; [3]Sanders et al Am J Crit Care Med 2010; [4]Marshall Am J Crit Care Med 2004; [5]Liou et al Am J Epidemiol 2001; [6]de Boer et al Thorax 2011

C-65

CF-301: Protocol Defined Pulmonary Exacerbations (PDPE) – Fuchs' Criteria

- Exacerbation treated with I.V. antibiotics plus ≥ 4 signs or symptoms
  - Change in sputum production
  - Dyspnoea
  - New or increased hemoptysis
  - Malaise, fatigue or lethargy
  - Fever (> 38°C)
  - Anorexia or weight loss
  - Sinus pain or tenderness
  - Change in sinus discharge
  - FVC or FEV_1 decreased by >10% from previous
  - Radiographic signs indicative of pulmonary infection
  - Increased cough
  - Changes in physical examination of the chest

Fuchs HJ, et al., N Engl J Med 331:637-642, 1994.

C-66

CF-301: Risk of Exacerbations Requiring I.V. Antibiotics are Reduced

		95% CI	% Reduction
Relative risk*	**0.65**	**0.42, 0.99**	**35**
Rate ratio	**0.74**	**0.46, 1.18**	**26**
Hazard ratio	**0.68**	**0.42, 1.11**	**-**

ITT population; *Post hoc

C-67

CF-301: Rescue Antibiotic Use and Hospitalizations

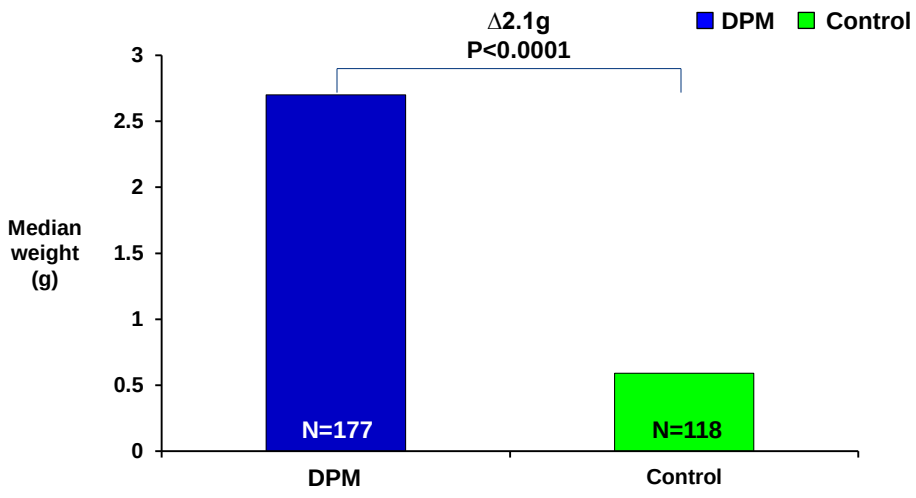
	Rate Ratio	95% CI	% Reduction
Rescue antibiotic use	0.66	(0.25, 1.76)	34
Hospitalizations	0.94	(0.26, 3.42)	6

ITT population

C-68

CF-301: Increase in Sputum Weight

Sputum Weight - 30 Minutes Post Study Drug – ITT Population



C-69

CF-302: Efficacy Results

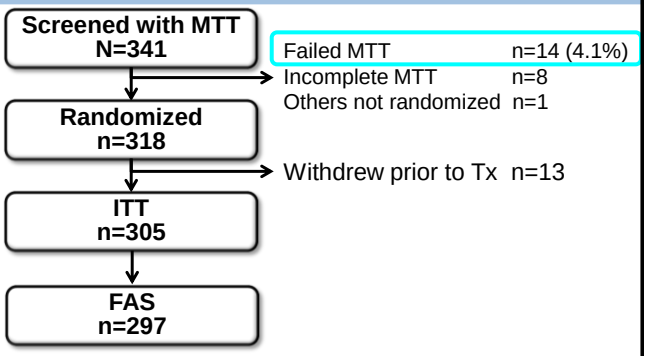
C-70

CF-302: Key Endpoints

- Primary efficacy
  - Change from baseline in FEV_1 over 26 weeks
- Key secondary efficacy
  - Other lung function parameters
  - FEV_1 in rhDNase users
  - Sputum weight
- Other secondary endpoints included pulmonary exacerbations (Fuchs' criteria)

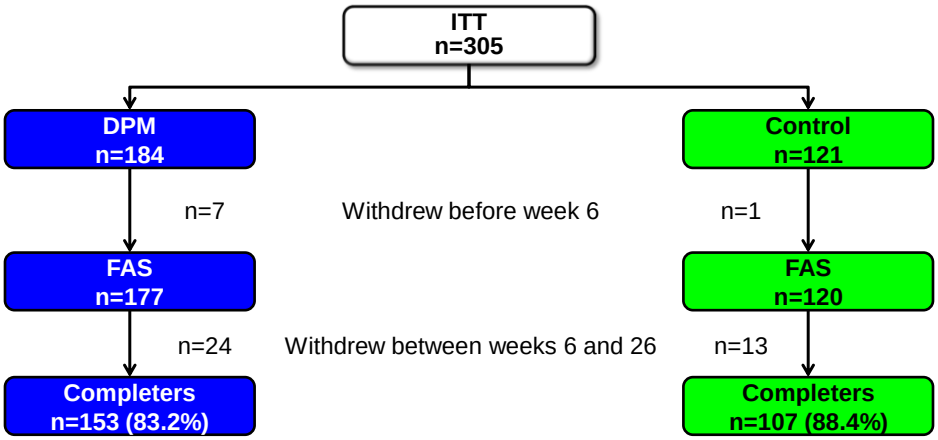
C-71

CF-302: Subject Disposition



C-72

CF-302: Subject Disposition



C-73

CF-302: Reasons for Withdrawal

	DPM N=184 (%)	Control N=121 (%)
Subject withdrew consent	7.1	5.8
Adverse event	7.1	4.1
Physician decision	1.1	0.8
Other	0.5	0.8
Protocol violation	0.5	0.0
Subject lost to follow-up	0.5	0.0
Subtotal	16.8	11.6

C-74

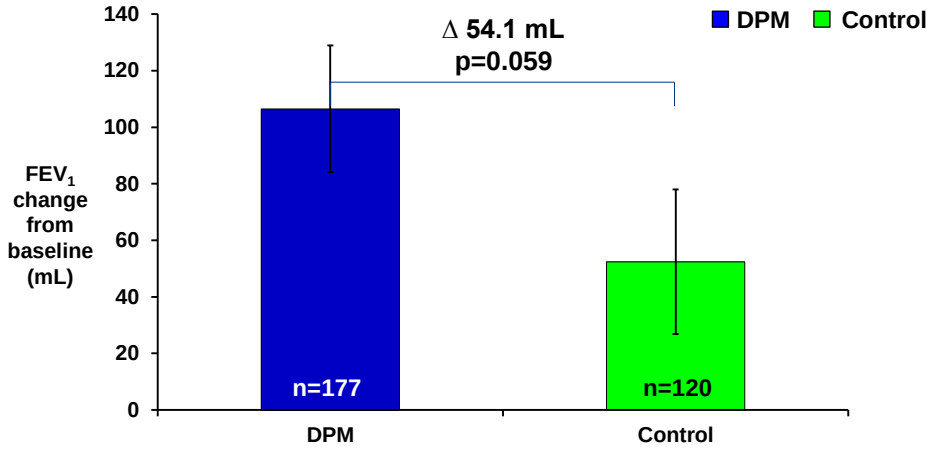
CF-302: Demographics

	CF-302 N=305	
Variable at Baseline (ITT population)	DPM N=184	Control N=121
Mean age years (SD)	19.6 (9.3)	20.4 (10.2)
Gender (female)	48.9%	47.9%
FEV_1 % predicted (SD)	65.2 (13.9)	64.4 (15.3)
FEV_1 volume (L) (SD)	2.06 (0.7)	2.0 (0.7)
Regular medication		
rhDNase	74.5%	76.0%
Inhaled/Nebulized Antibiotics	56.5%	57.9%

C-75

CF-302: Primary Endpoint Results- Clinically Meaningful Improvement in Lung Function

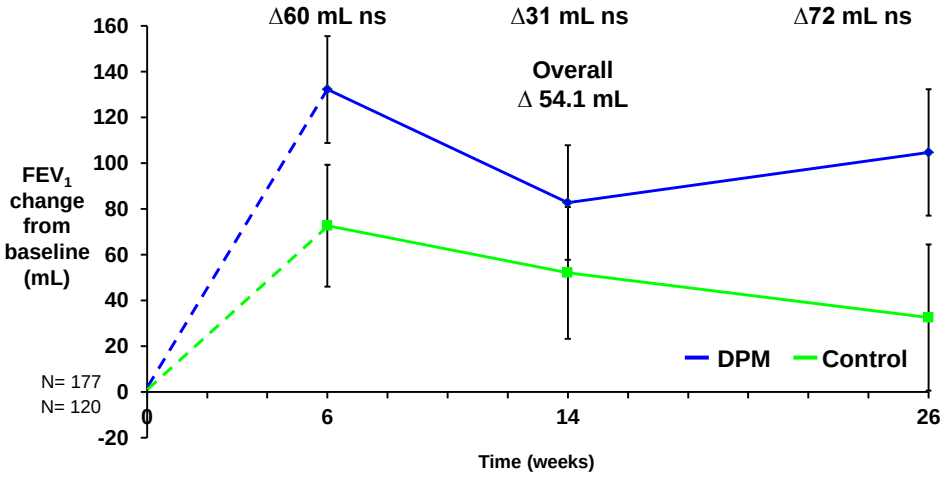
Overall Effect Size (FEV_1) over 26-weeks- FAS Population



Error bars represents ±SEM; Model = MMRM

C-76

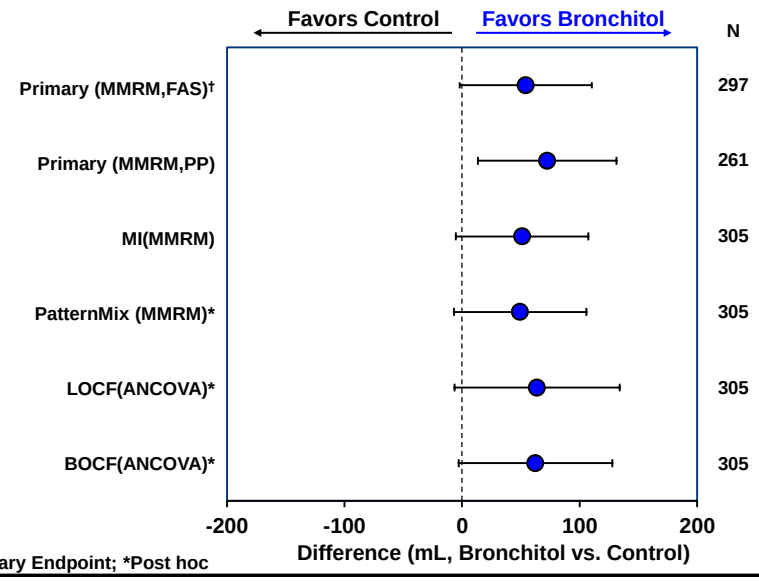
CF-302: Change in FEV_1 Over Time



FAS population; ns=not significant; Error bars represents ±SEM; Model = MMRM

C-77

CF-302: Sensitivity Analyses for FEV_1



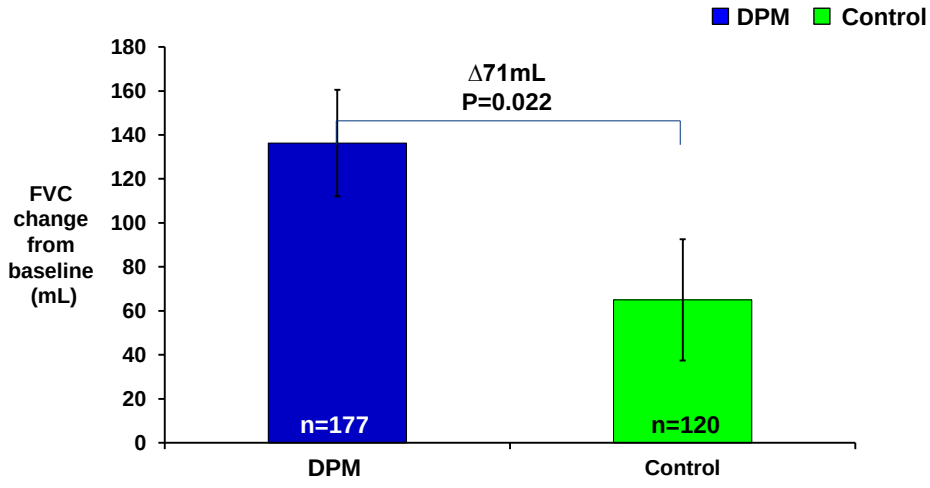
†Primary Endpoint; *Post hoc

C-78

CF-302: Secondary Endpoints

C-79

CF-302: FVC Change from Baseline



FAS population; Error bars represents ±SEM; Model = MMRM

C-80

CF-302: Trends Supportive of Exacerbation[1] Reduction

		95% CI	% Difference
Relative risk*	0.80	0.48, 1.32	20
Rate ratio	0.85	0.51, 1.41	15
Hazard ratio	0.74	0.42, 1.32	-

ITT population; *Post hoc; [1]Fuchs et al, 1994.

C-81

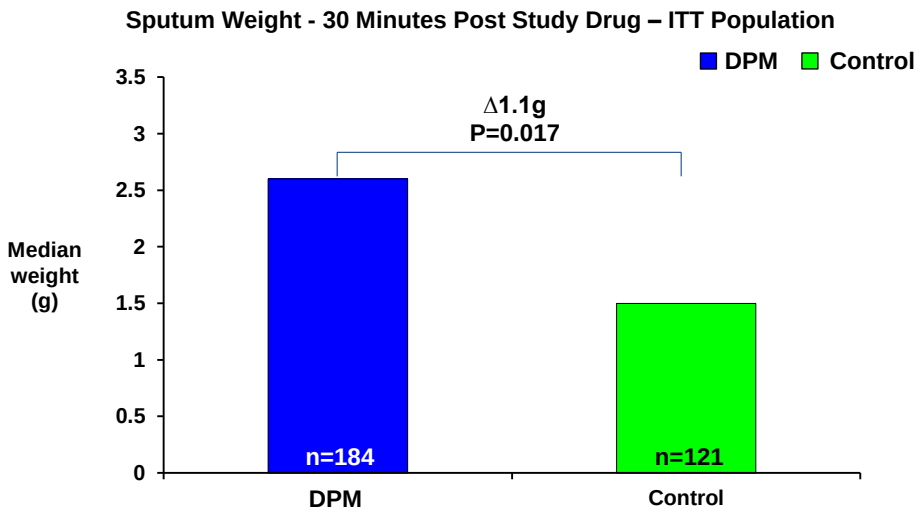
CF-302: Rescue Antibiotic Use and Hospitalizations

	Rate Ratio	95% CI	% Reduction in Rate (Rate Ratio)
Rescue antibiotic use	0.89	(0.69, 1.15)	11
Hospitalizations	0.75	(0.42, 1.33)	25

ITT population

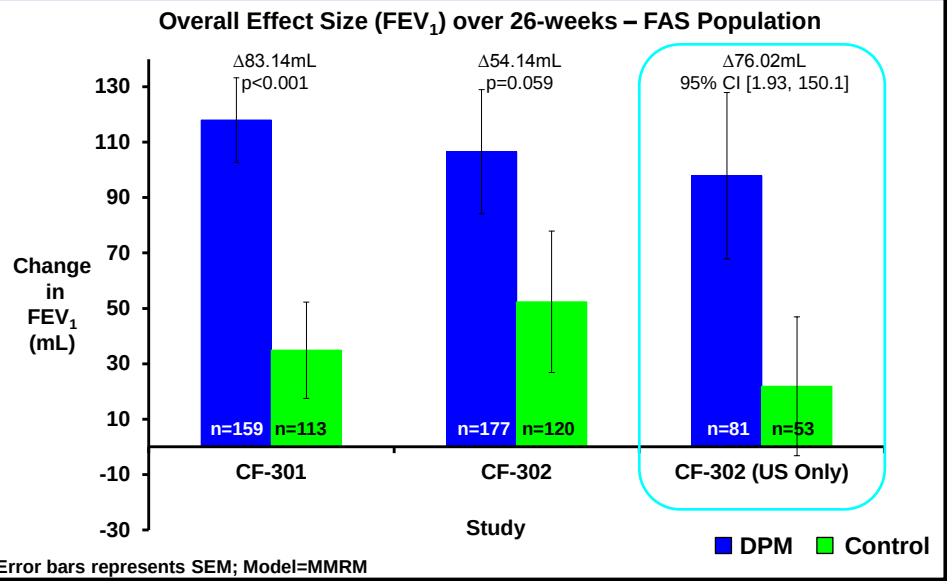
C-82

CF-302: Increase in Sputum Weight



C-83

Clinically Meaningful Improvement in Lung Function: Post-hoc US Population



Error bars represents SEM; Model=MMRM

C-84

Pooled Phase 3 Data: Subgroup Analysis

C-85

Pooled Phase 3 Data: Subgroup Analyses

- Efficacy established based on overall population
- Studies not powered to assess efficacy by subgroup

C-86

Pooled Phase 3 Data: No Significant Interaction Terms

Subgroup	Interaction Between Treatment and Pooled Subgroup (p-value)
rhDNase use	0.459
Age group	0.216
Disease severity	0.279
Gender	0.337

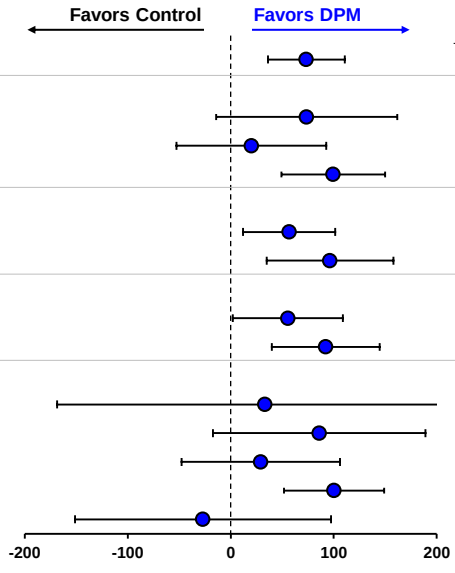
C-87

Pooled Phase 3 Data: Heterogeneous Response Unlikely

- No significant interaction terms
- Mode of action based on improved muco-ciliary clearance applicable to all patients

C-88

Pooled Phase 3 Data: Effect Size (FEV_1 mL) by Subgroup



	Total	DPM	Control
All	569	336	233
Age			
Children	103	62	41
Adolescents	149	86	63
Adults	317	188	129
rhDNase			
Users	373	220	153
Non-users	196	116	80
Sex			
Female	272	155	117
Male	297	181	116
Severity (% Predicted)			
>90%	18	11	7
>80-90%	74	49	25
>70-80%	123	73	50
>40-70%	307	176	131
≤40%	47	27	20

Post hoc

Model = MMRM

C-89

Efficacy Summary

- Meaningful and sustained FEV_1 improvements in both phase 3 studies
  - CF-301: 83.1mL change: $p<0.001$
  - CF-302: 54.1mL change: $p=0.059$
- Supportive trends in exacerbation reduction
- Supportive FVC and sputum weight evidence
- Clinically meaningful benefit added to standard of care

C-90

Safety

Brett Charlton, MD, PhD
Medical Director
Pharmaxis

C-91

Total Patients Studied in DPM CF Program[1]

Clinical Trials	Children (n)	Adults (n)	Total (n)
Phase 2 (201, 202 & 203)	76	37	113
Phase 3 (301 & 302)[1]	259	341	600
Total CF patients	335	378	713

[1]Includes DPM and control patients

C-92

DPM Phase 3 Safety Data Set in Patients with CF (301 & 302)

- 541 patients treated with DPM in phase 3 safety analysis
  - 361 patients during double-blind
  - 180 ex-control patients in open label phase
  - 370 patient years of DPM exposure
- 240 patients with ≥ 48 weeks of DPM
  - No new safety signals

C-93

Only Ingredient in DPM is Mannitol

- Generally Recognized as Safe (GRAS)
- DPM safety is focused on local lung effects

C-94

No Clinically Meaningful Changes in Vital Signs or Lab Results

- No significant changes between baseline and week 26 in vital signs, weight, or SpO_2
- Laboratory abnormalities similar in both treatment groups

C-95

Microbiology Data from Phase 3 Trials

- No evidence of increased microorganism growth with inhaled mannitol in CF
- Qualitative microbiology
  - No difference in proportion of subjects with abnormal flora at week 26 compared to baseline

C-96

AEs Reported in ≥ 5% of Subjects

	Pooled 301 & 302	
Preferred Term	DPM N=361 (%)	Control N=239 (%)
Subjects with ≥ 1 AE	**88.4**	**90.0**
Condition aggravated	36.8	40.2
Cough	21.1	16.7
Headache	17.7	20.9
Pharyngolaryngeal pain	12.2	7.5
Bacteria sputum identified	10.8	11.3
Nasopharyngitis	10.2	9.6
Hemoptysis	9.4	5.4
Upper respiratory tract infection	6.6	7.9
Pyrexia	6.6	6.3
Vomiting	6.1	2.5
Lower respiratory tract infection	6.1	10.0
Abdominal pain	5.5	7.1

C-97

Most AEs were Mild or Moderate

	Phase 3 Controlled Studies[1] Double-blind Period	
	DPM 400mg Events=1544 (%)	Control Events=979 (%)
Mild AE	56.3	52.1
Moderate AE	37.3	39.1
Severe AE	6.4	8.8

[1]Studies 301 and 302, 26 weeks

C-98

SAEs Reported in ≥ 1% Subjects

	Phase 3 Controlled Studies[1] Double-blind Period	
	DPM 400mg N=361 (%)	Control N=239 (%)
≥ 1 SAE	21.3	27.2
Condition aggravated	16.6	18.8
Hemoptysis	2.2	0.8
Lower respiratory tract infection	1.1	2.1

[1]Studies 301 and 302, 26 weeks

C-99

Discontinuation Due to Adverse Events

	Phase 3 Controlled Studies[1] Double-blind Period	
	DPM 400mg N=361 (%)	Control N=239 (%)
AE leading to discontinuation	11.4	6.3
Cough	5.0	2.5
Condition aggravated	2.2	1.3
Hemoptysis	1.7	0.0

[1]Studies 301 and 302, 26 weeks

C-100

Reported AEs were Similar by Age

	Pooled 301 & 302			
	6-17 years		≥18 years	
	DPM N=154 (%)	Control N=105 (%)	DPM N=207 (%)	Control N=134 (%)
Subjects with ≥1 AE	92	95	86	86
Subjects with ≥1 SAE	20	28	23	27
Subjects with ≥1 AE leading to discontinuation	6	3	19	9

[1]Studies 301 and 302, 26 weeks

C-101

Identified AEs of Interest

- Known or suspected risk associated with DPM or aerosol treatments and more frequently observed in CF disease state
  - Bronchospasm
  - Cough
  - Hemoptysis

C-102

Change in FEV_1 During MTT

- Total number of patients screened = 719
- Fall in FEV_1 > 20%: 5.7%
  - Mean fall in FEV_1 for failed MTT: 25.6%

Studies 301 and 302

C-103

AEs Possibly Associated with Bronchoconstriction

	Phase 3 Controlled Studies[1] Double-blind Period	
	DPM 400mg N=361 (%)	Control N=239 (%)
Asthma	0.6	1.3
Asthmatic crisis	0.0	0.4
Bronchospasm	0.6	0.0
Chest discomfort	2.8	1.7
Wheezing	1.7	2.1

[1]Studies 301 and 302, 26 weeks

C-104

Risk Mitigation: MTT Challenge and Boxed Warning

- Mandatory mannitol tolerance test
  - Exclusion from treatment for those with failed test
- Proposed boxed warning on severe bronchospasm

C-105

Cough Events in DPM Studies

	Phase 3 Controlled Studies[1] Double-blind Period	
	DPM 400mg N=361 (%)	Control N=239 (%)
Cough	**21.1**	**16.7**
Severe	**2.2**	**1.7**
Study withdrawal	**5.0**	**2.5**

[1]Studies 301 and 302, 26 weeks

C-106

Hemoptysis is a Common Event in CF Patients

- Commonly associated with pulmonary exacerbations
- Blood in sputum may range from small streaks to large amounts
- Events are usually mild
- Incidence reported to increase with disease severity and age

Flume, P, Am. J. Respir. Crit. Care Med. vol. 182 no. 3, 298-306, 2010.

C-107

Hemoptysis AEs

	Phase 3 Controlled Studies[1] Double-blind Period	
	DPM 400mg N=361 (%)	Control N=239 (%)
Hemoptysis AEs	**9.4**	**5.4**

- Median duration of events less than one day
- All events resolved

[1]Studies 301 and 302, 26 weeks

C-108

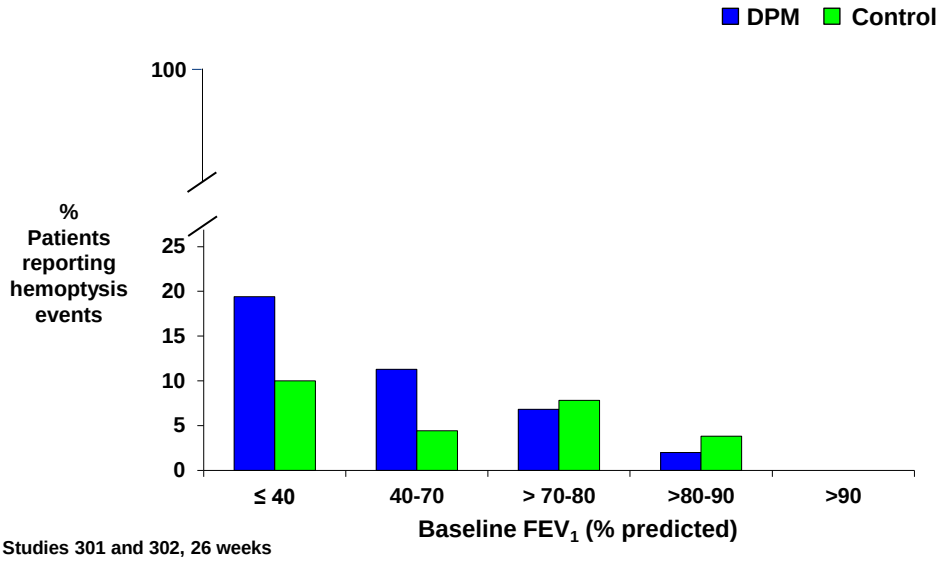
Hemoptysis AEs

	Phase 3 Controlled Studies[1] Double-blind Period	
	DPM 400mg N=361 (%)	Control N=239 (%)
Event Severity		
Mild	**52.5**	**76.9**
Moderate	**37.5**	**15.4**
Severe	**10.0**	**7.7**

[1]Studies 301 and 302, 26 weeks

C-109

Association Between Hemoptysis and Disease Severity



Studies 301 and 302, 26 weeks

C-110

Hemoptysis Reported as AE and as Part of an Exacerbation

- Hemoptysis in CF is frequently a component of exacerbations
- Some exacerbation-related hemoptysis events were not recorded separately as AEs
- Assessment of risk for hemoptysis should include
  - Hemoptysis reported as an AE
  - Hemoptysis reported as a component of an exacerbation (but not separately reported as an AE)

C-111

All Reported Hemoptysis Cases

	Phase 3 Controlled Studies[1] Double-blind Period			
Subject Group	DPM 400mg N=361		Control N=239	
All subjects	n	%	n	%
Reported as AE	34	9.4	13	5.4
Part of exacerbation (not hemoptysis AE)	14	3.9	19	7.9
Total	48	13.3	32	13.4

[1]Studies 301 and 302, 26 weeks

C-112

Hemoptysis by Age

	Phase 3 Controlled Studies[1] Double-blind Period			
Subject Group	DPM 400mg N=154		Control N=105	
Children 6-17 years old	n	%	n	%
Reported as AE	12	7.8	2	1.9
Part of exacerbation (not hemoptysis AE)	4	2.6	6	5.7
Total	16	10.4	8	7.6
Adults ≥ 18 years old	N=207		N=134	
Reported as AE	22	10.6	11	8.2
Part of exacerbation (not hemoptysis AE)	10	4.8	13	9.7
Total	32	15.5	24	17.9

[1]Studies 301 and 302, 26 weeks

C-113

Hemoptysis Reported in Patients with Risk Factors (6-17 years)

Age	FEV_1 (% pred)	Adverse Event Severity	Part of Pulmonary Exacerbation	History of Hemoptysis	Infectious Risk Factors
9	57	Mild	✓	✓	Aspergillus
10	46	Mild	✓		Staph. a
10	65	Severe		✓	Staph. a
11	77	Mild	✓		Staph. a
12	44	Mod			Aspergillus
13	32	Mod/SAE	✓	✓	Staph. a
14	78	-	✓		Staph. a
15	47	-	✓	✓	
15	68	Mild	✓	✓	
16	36	Mild/SAE	✓	✓	Staph. a
16	45	Mod	✓	✓	
16	41	Mild	✓	✓	Staph. a
16	78	Mild	✓	✓	Aspergillus
17	60	Severe/SAE	✓	✓	
17	86	-	✓		Staph. a
17	81	-	✓		Staph. a

C-114

Hemoptysis Outcome in Patients Aged 6-17 Years

- 10/12 patients with hemoptysis AE reported as mild/moderate events
- 3 SAEs
- All events resolved
- No study withdrawals due to event

C-115

Incidence of Massive Hemoptysis Consistent with Disease

- 6 month incidence
  - DPM = 0.6% (n=2)
  - Control = 0.4% (n=1)
- 1 incident in open label phase
- Incidence of massive hemoptysis consistent with background rate from registry data[1]
  - Expected 0.4% - 1.4%

[1]Flume et al, US registry data (0.87%/yr), 2005; Belgian registry BMR (2.7%/yr), 2009.

C-116

Hemoptysis Information in Proposed Label

- Pharmaxis guidance for physicians (consistent with current CFF guidelines)
  - Careful monitoring of patients
  - Discontinuation of DPM
  - Withhold DPM in the event of massive hemoptysis
- Limitation for patients with FEV_1 below 40%
  - Benefit-risk not established

C-117

Risk Minimization

- Limited distribution
  - Through specialty CF pharmacies
- Medical education and training for HCP
  - Provided by Pharmaxis staff
  - Guidance for minimizing and managing risk of hemoptysis
- Pharmacovigilance
  - Questionnaires sent to reporting HCP to collect detailed information for hemoptysis
  - Information periodically assessed to guide risk assessment

C-118

Post-approval Actions to Evaluate Hemoptysis in Children

- Pharmaxis is committed to post-approval action
- CF expert discussions support that a registry program is appropriate for gathering hemoptysis data and assessing ongoing risk
  - Exploring use of CFF database
  - Similar format to European DPM registry
- Plan to discuss with FDA, including feedback from PADAC

C-119

Clinical Data Support the Safety of DPM

- Safety evaluated through extensive body of data
- Mannitol is a GRAS product
- AEs mostly represent tolerability issues
- Hemoptysis will be addressed in label and post-approval activities

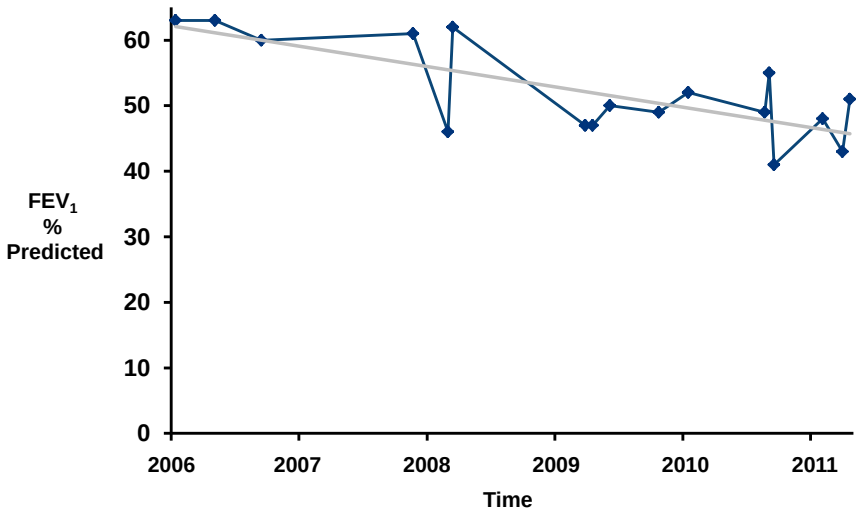
C-120

DPM: A Clinician's Perspective

Patrick A. Flume, MD
Professor of Medicine and Pediatrics,
Pulmonary and Critical Care Medicine
Medical University of South Carolina

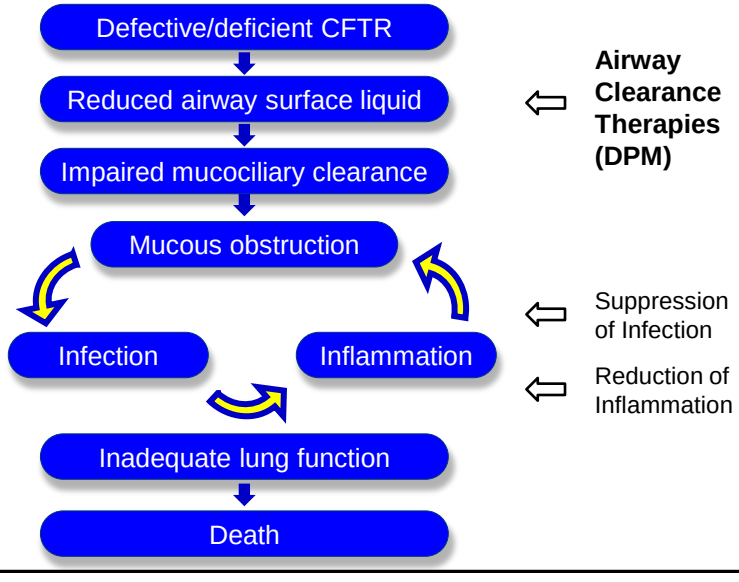
C-121

Pulmonary Function Decline: Patient Example



C-122

Focus on Improving Airway Clearance



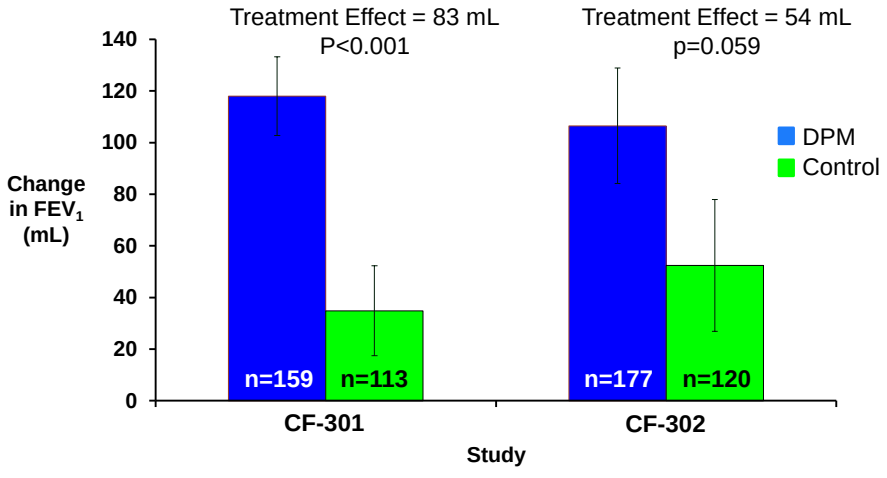
C-123

How the CF Clinician Looks at a New Therapeutic Option

- Efficacy
- Safety
- How will I introduce the therapy into my patient's current regimen?

C-124

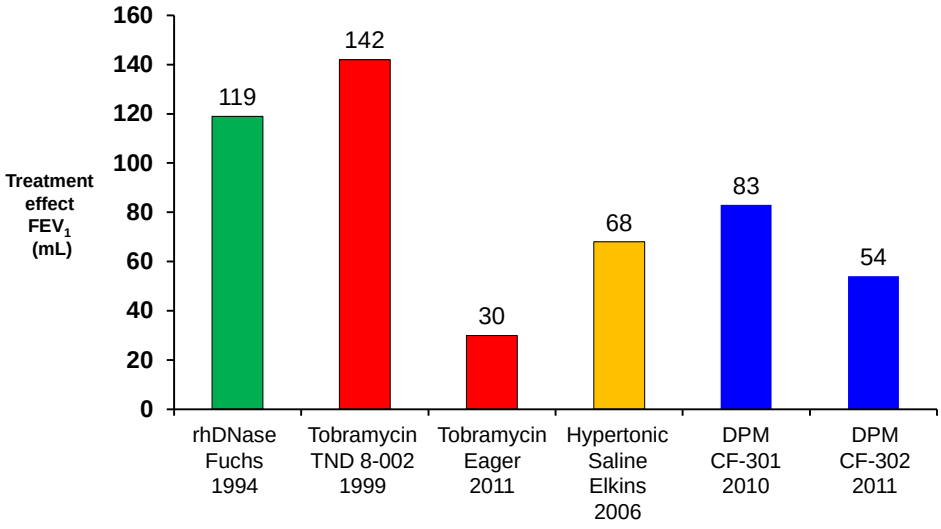
Clinically Meaningful Improvement in Lung Function[1]



[1]Primary Endpoint, MMRM; Error bars represents SEM

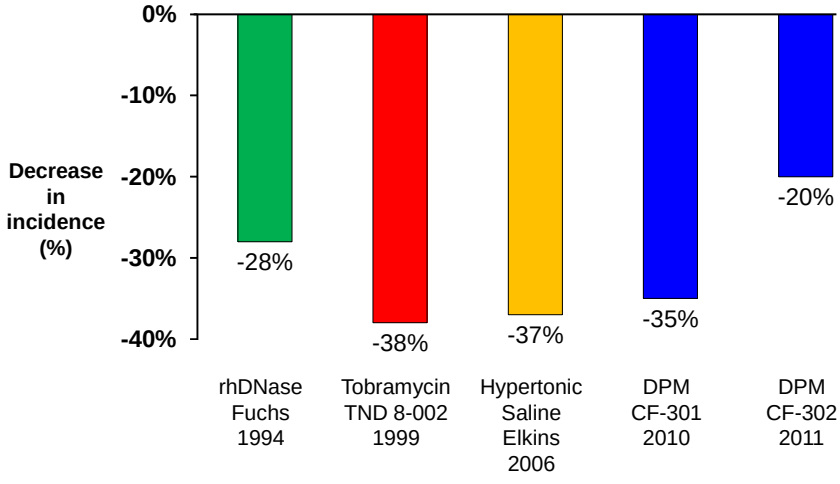
C-125

Historical Data Provide Context for Clinically Meaningful FEV_1 Improvement



C-126

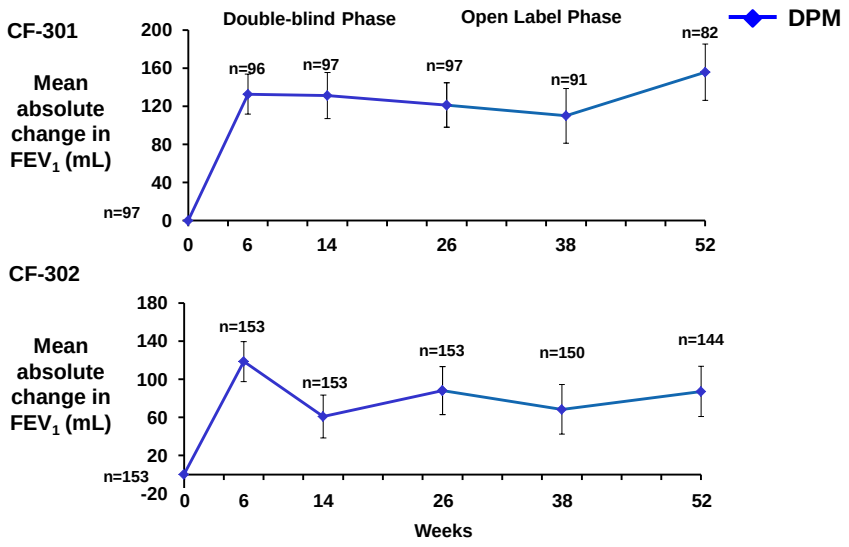
Comparison of Exacerbation Incidence



C-127

CF-301 & 302 12-month FEV_1 Data

Summary Data of Mean Change (mL) Over Time



Error bars represents ±SEM

C-128

How the CF Clinician Looks at a New Therapeutic Option

- Efficacy
- Safety
  - Bronchospasm
  - Hemoptysis
- How will I introduce the therapy into my patient's current regimen?

C-129

MTT Helps Identify Patients with Bronchial Hyper-responsiveness

- Few experience bronchospasm if pass MTT
- Pre-treatment bronchodilator further reduces risk

C-130

Hemoptysis is a Common Event Among Patients with CF

Source	Time	Incidence of Hemoptysis
Retrospective report[1]	1 year	9%
Placebo arm rhDNase[2]	6 months	21%
Placebo arm Tobramycin[3]	6 months	31%
Placebo arm Ivacaftor[4]	12 months	22%
DPM (301 & 302)	6 months	9.4%

[1]Efrati et al, 2008
[2]Fuchs et al, 1994
[3&4]Ramsey et al, 1999 & 2012

C-131

Massive Hemoptysis is Far Less Common Among Patients with CF

Source	Time	Incidence of Hemoptysis
DPM	6 months	0.6%
US registry[1]	1 year	0.9%
Belgium registry[2]	1 year	2.7%

[1]Flume et al, US registry data, 2005; [2]Belgian registry BMR, 2009.

C-132

Hemoptysis is a Common Aspect of CF Lung Disease

- CFF Guidelines dedicated to hemoptysis
  - Monitor for events and quantify bleeding
- Hemoptysis is typically treated as sign of an exacerbation
- Management of massive hemoptysis
  - Withhold aerosol and airway clearance therapies
  - Restart at resolution

C-133

Hemoptysis in Patients < 18 Years of Age

- Hemoptysis signal in younger patients
- Pediatric patients with hemoptysis had severe lung disease
- Hemoptysis was not persistent, with no episodes of massive hemoptysis
- No patients withdrew from trial as a result of a hemoptysis event
- Median FEV_1 improvement of 60 mL

[a] Studies 301 and 302, 26 weeks

C-134

Other than Hemoptysis, DPM AEs Appear to be Tolerability Related

- Withdrawals due to tolerability is common with CF aerosol therapies
- Completer analysis provides evidence of efficacy for patients that stay on therapy

C-135

How the CF Clinician Looks at a New Therapeutic Option

- Efficacy
- Safety
- How will I introduce the therapy into my patient's current regimen?

C-136

Advantages of DPM Therapy

- Low treatment burden
  - Portable
  - ~ 5 minute treatment
  - Minimal set-up
  - Minimal cleaning
  - No refrigeration required
- Fits lifestyle of patients
  - Discrete
  - Convenient

C-137

Updated CF Pulmonary Guidelines

- For patients with CF ≥ 6 years that pass MTT the CFF recommends the chronic use of inhaled mannitol to improve lung function and reduce pulmonary exacerbations[1]

[1]Accepted for publication, Am J Respir Crit Care Med

C-138

DPM is Supported by the Totality of the Evidence

- Clearance of airway secretions is key to the treatment of CF airways disease
  - For both adult and pediatric patients
- DPM improves lung function and reduces the frequency of pulmonary exacerbations
  - Consistent efficacy trends
  - Provides benefit when added to current therapy
- Safety profile for DPM is acceptable

C-139

Dry Powder Mannitol (DPM)

Pharmaxis
Pulmonary and Allergy Drugs Advisory Committee
January 30, 2013