

pharmaxis

# Therapeutic products for respiratory diseases

March 2010






# Forward Looking Statements

---

This presentation may contain forward-looking statements that are based on management's current expectations and beliefs and are subject to a number of factors and uncertainties that could cause actual results to differ materially from those described in the forward-looking statements. The forward-looking statements contained in this presentation include statements about future financial and operating results, results of our clinical trials, status of our regulatory submissions, possible or assumed future growth opportunities and risks and uncertainties that could affect Pharmaxis' product and products under development. These statements are not guarantees of future performance, involve certain risks, uncertainties and assumptions that are difficult to predict, and are based upon assumptions as to future events that may not prove accurate. Therefore, actual outcomes and results may differ materially from what is expressed herein. In any forward-looking statement in which Pharmaxis expresses an expectation or belief as to future results, such expectation or belief is expressed in good faith and believed to have a reasonable basis, but there can be no assurance that the statement or expectation or belief will result or be achieved or accomplished.

We are not under any duty to update forward-looking statements unless required by law. This investor presentation is not an offer of the sale of securities.

# Company Overview

Objective	The development of products for respiratory and inflammatory diseases
Lead products	Aridol: management of asthma and COPD Bronchitol: therapeutic for cystic fibrosis and COPD ASM8: therapeutic for asthma
Discovery	PXS25 (M6P receptor blocker); PXS4159 (VAP1 inhibitor)
Listing	ASX (Nov 2003): PXS
Locations	Sydney, Australia • Exton, USA • Luton, UK • Montreal, Canada
Facility	GMP Manufacture of lead products
Employees	136
Cash (31/12/09)	A\$102 million
Shares & Options	Shares outstanding: 222m; Options outstanding: 13m
Key patents	Bronchitol & Aridol granted in USA, Australia, Asia, Canada, Japan; pending in EU, Japan.
Analyst coverage	    

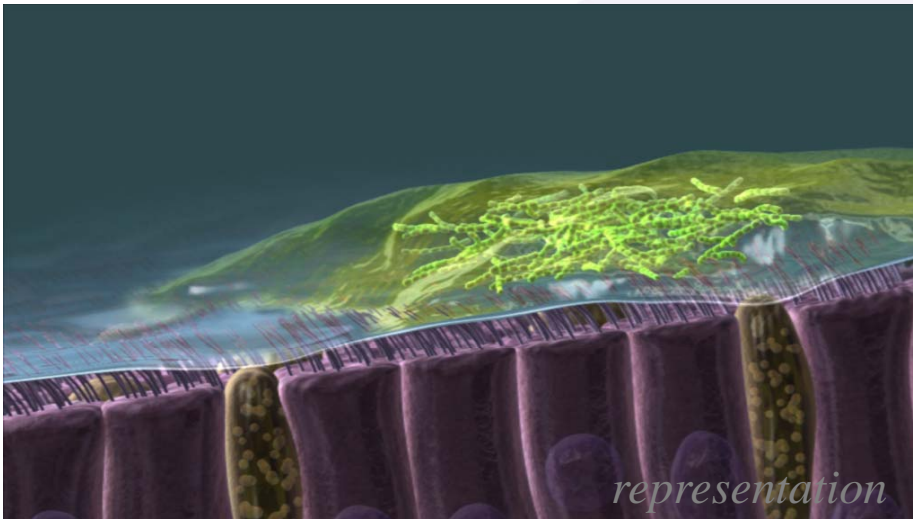


# Bronchitol for Cystic Fibrosis



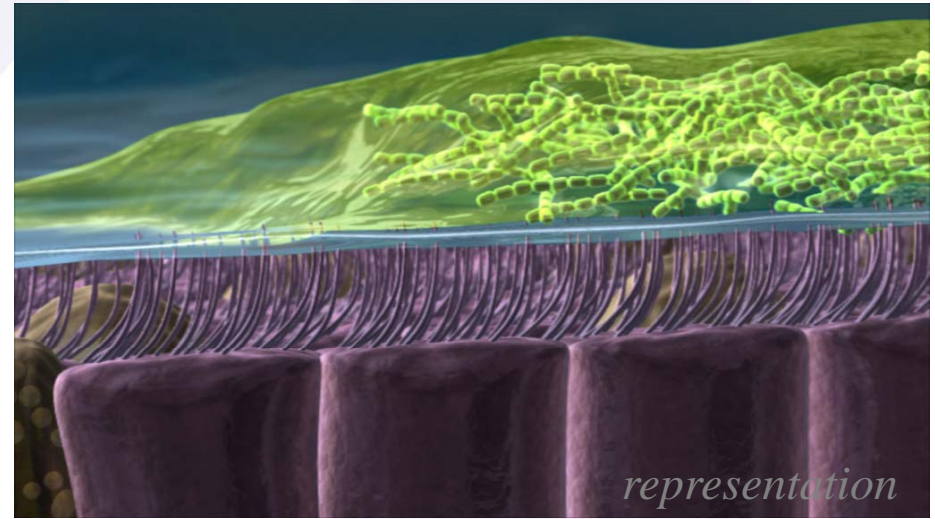
# Osmotic clearance of abnormal mucus

Before treatment



Lung surface dehydrated  
Airway surface fluid layer impaired  
Lung defense and hygiene compromised

After Bronchitol administration



Lung hydrated  
Airway surface liquid restored  
Normal lung clearance

# Bronchitol – cystic fibrosis



- **Background**

- Genetic disorder affecting 75,000 worldwide (30,000 in US)
- Poorly hydrated, tenacious, thick mucus
- Current life expectancy is 37 years (US)



- **Current treatments: rhDNase and tobramycin**

- Delivered by nebulizer (preparation, sterilization)
- rhDNase (Pulmozyme®): global sales US\$460mm (2009)
- Tobramycin (Tobi®): global sales US\$233mm (2007)



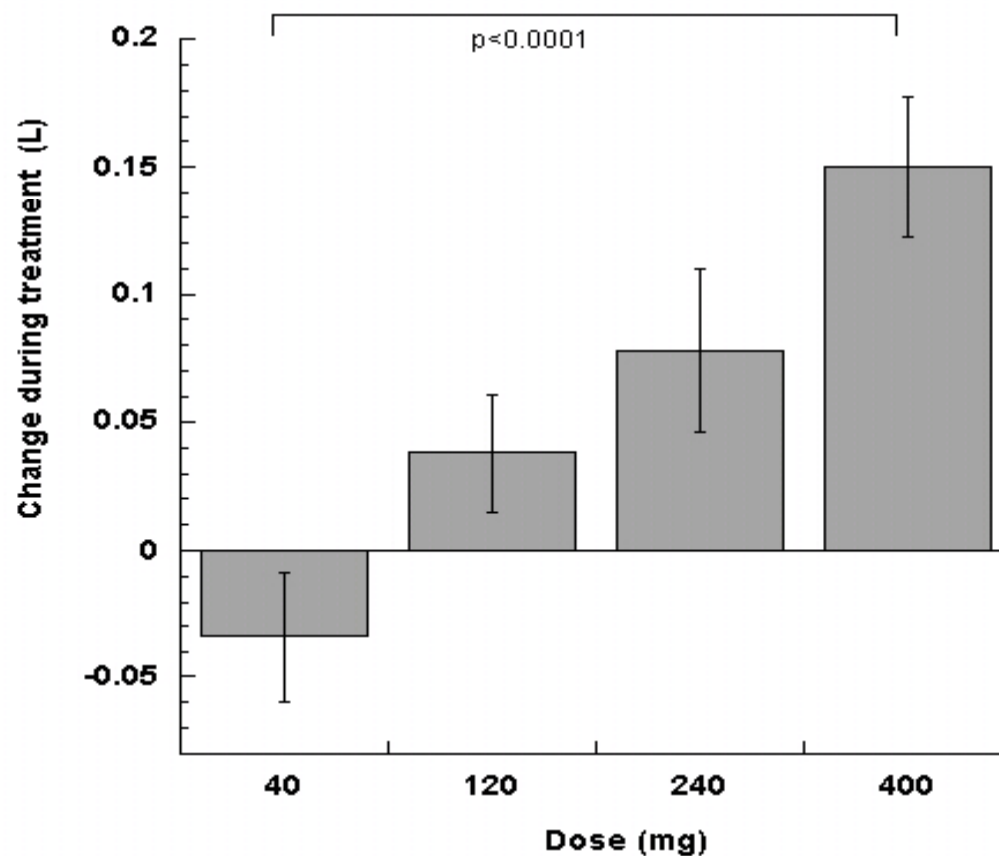
# Treatment Progression – CFF Guidelines

Grade of recommendation	Mild	Moderate/Severe
A Benefit is substantial	-	rhDNase Inhaled tobramycin (if p.a. present)
B Benefit is moderate	rhDNase Inhaled tobramycin (if p.a. present) Azithromycin (if p.a. present) Hypertonic Saline Ibuprofen (FEV1>60%) Inhaled B2 agonists	Hypertonic Saline Azithromycin (if p.a. present) Ibuprofen (FEV1>60%) Inhaled B2 agonists
Insufficient evidence	Other inhaled antibiotics Oral corticosteroids (18+ yr olds) Leukotriene inhibitors / cromolyn sodium. Anticholinergic bronchodilators N-acetylcysteine	
Against	Inhaled corticosteroids (if asthma / ABPA absent) Oral corticosteroids (6-18 yr olds)	

**There remains a lack of quality long term studies evaluating existing treatments used in CF**



# CF-202 Dose Response



- 48 subjects
- Open label, crossover multidose study
- 400mg twice a day, then 40, 120, 240mg twice a day for 14 days in a random order
- Washout between doses

# Bronchitol – cystic fibrosis registration

- **1<sup>st</sup> Pivotal Phase III trial**

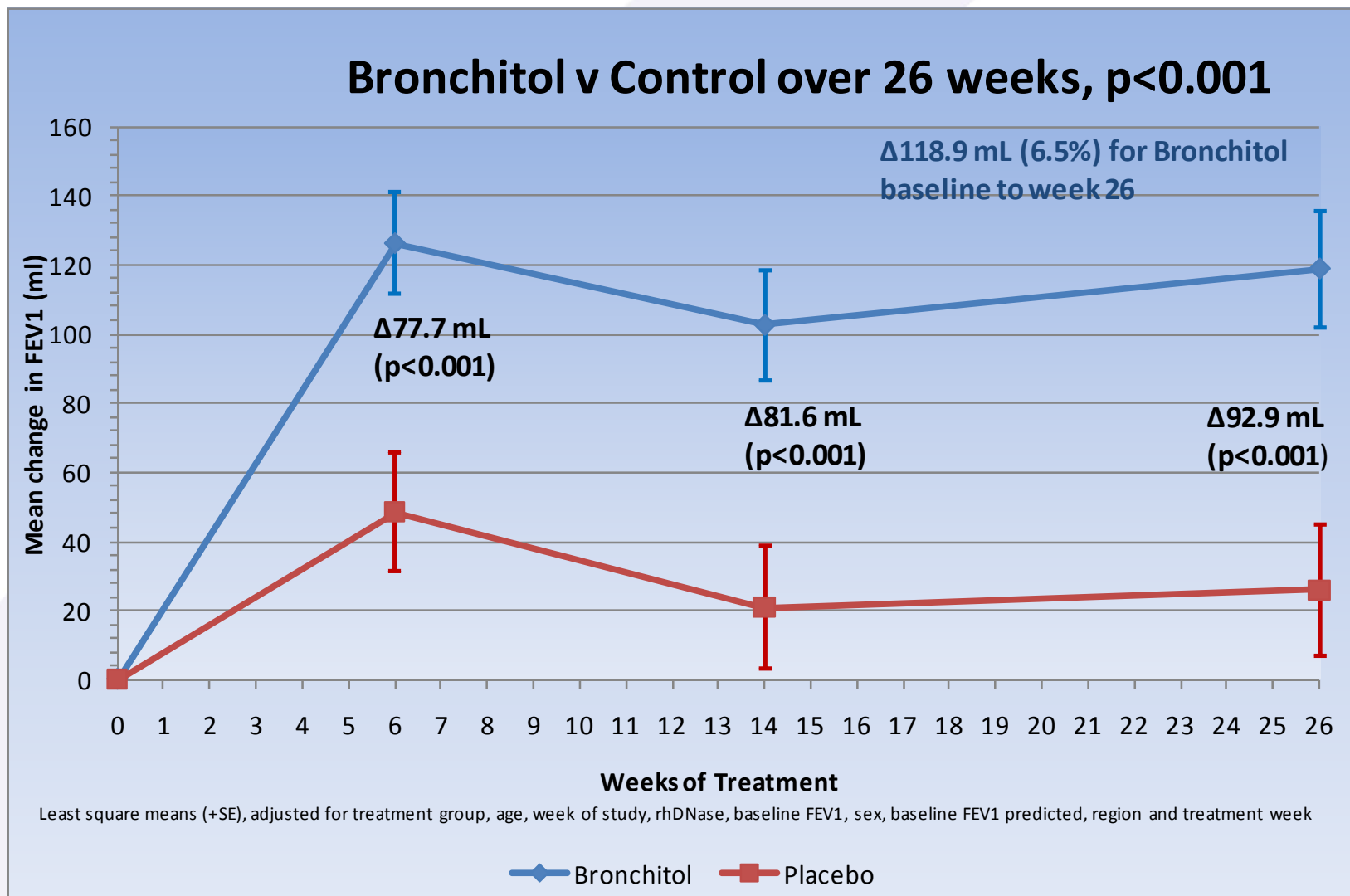


- Multicentre, double blind, placebo controlled
- 325 subjects greater than 6 years old
- 6 month treatment, 400mg twice per day followed by 6 month open
- Primary endpoint:
  - lung function (FEV1)
- Key secondary endpoint:
  - Lung function (FEV1) in patients on rhDNase
- Other endpoints
  - exacerbations
  - antibiotic use
  - QOL and safety

## First Phase 3 -Key demographics at baseline

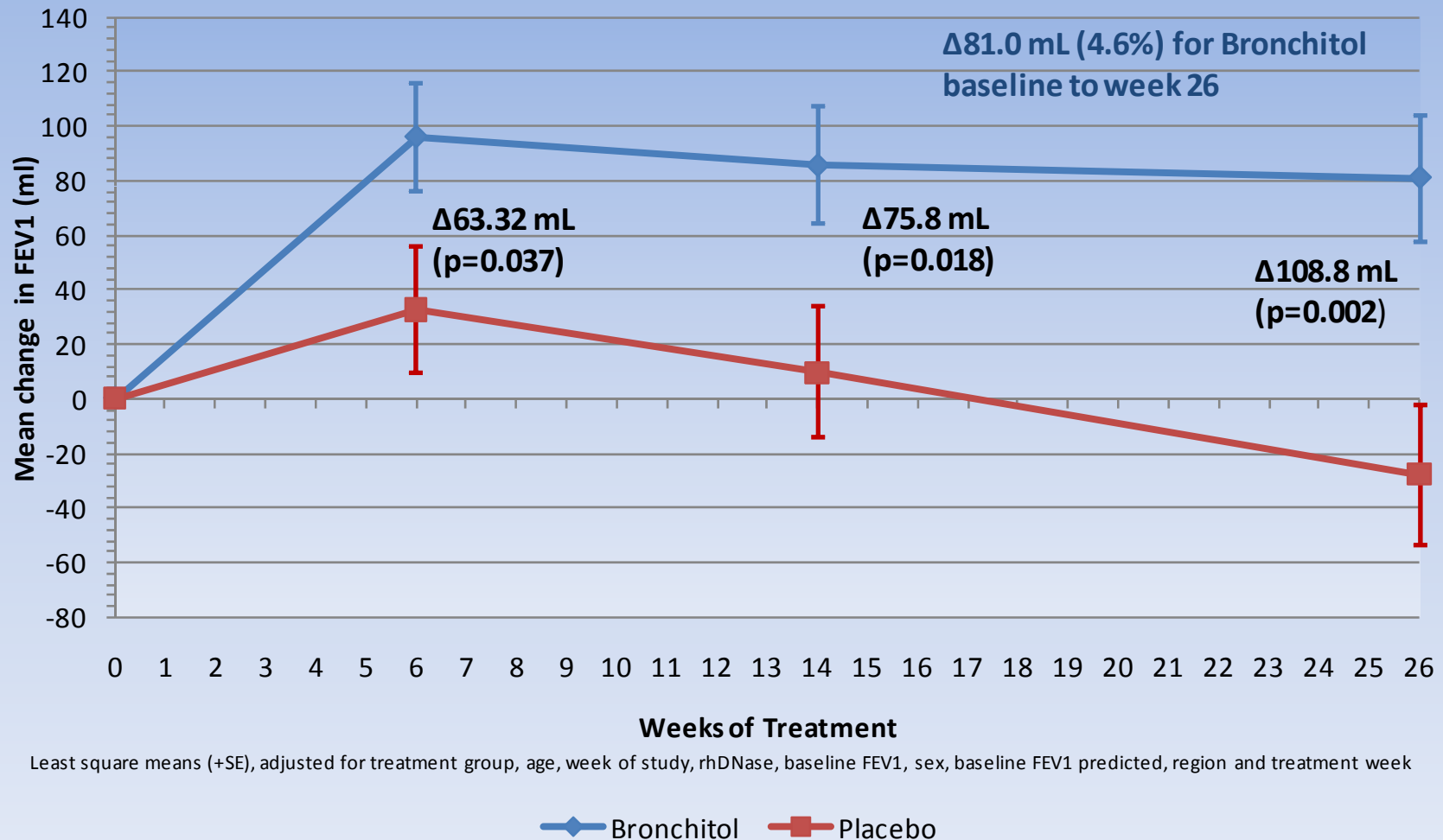
	Bronchitol n = 177	Placebo n = 118
Mean age (years)	23.1	22.8
6 – 11 years	18%	14%
12 – 17 years	18%	21%
>18 years	64%	65%
Gender: Female	40.1%	51.7%
BMI; mean (SD) kg/m <sup>2</sup>	21.1 (4.0)	20.4 (3.6)
FEV1; mean (range)		
L	2.07 (0.71, 4.92)	1.95 (0.78, 3.75)
% of predicted	62.4% (26, 93)	61.4% (30,94)
Regular medication		
RhDNase; n (%)	96 (54.2%)	67 (56.8%)
Antibiotics	94.8%	90.2%
B <sub>2</sub> agonists	83.9%	87.1%

# CF-301 Absolute mean change (mL) in FEV<sub>1</sub>

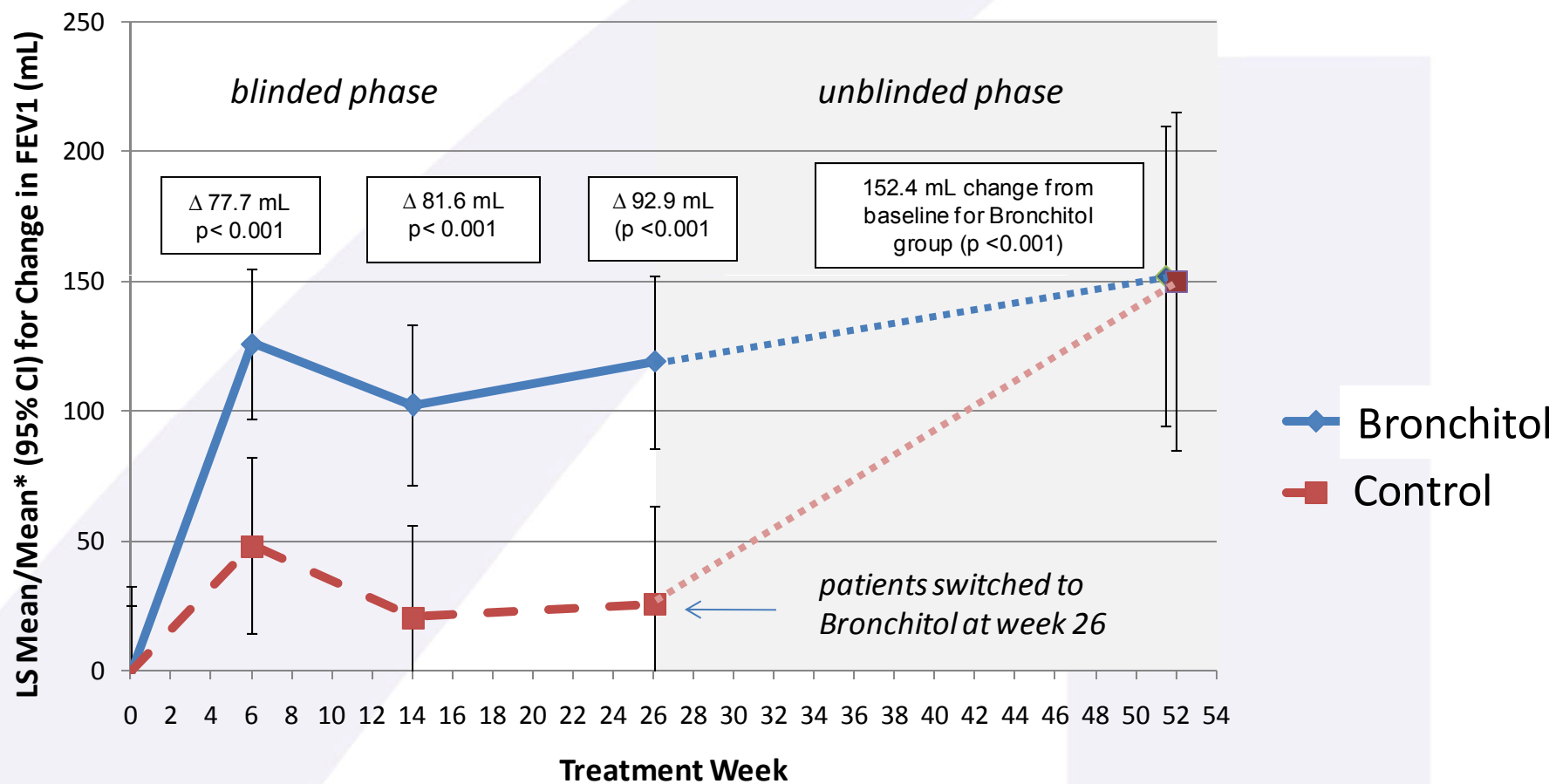


# CF301 Absolute mean change (mL) in FEV<sub>1</sub> (rhDNase users)

## Bronchitol v Control over 26 weeks, p<0.001

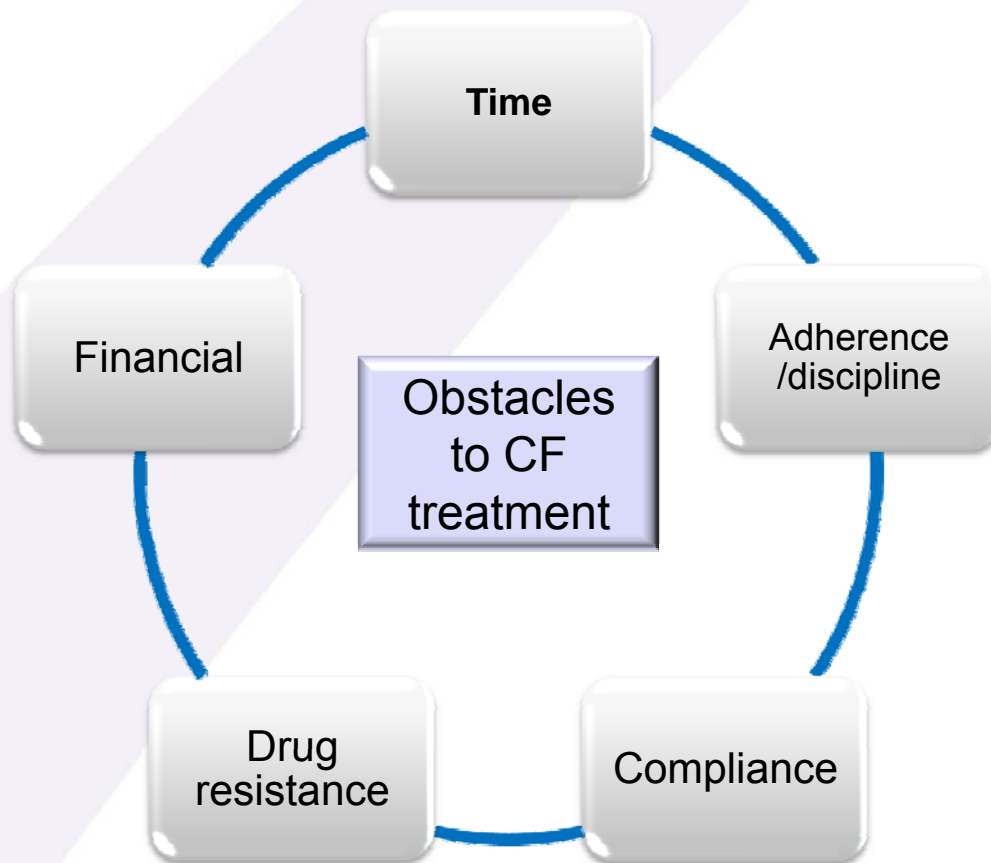


# CF301 – lung function changes at 12 months



# Cystic Fibrosis market research

The time commitment to treatment is the biggest challenge to physicians and patients



- Time requirements and adherence to therapy are pervasive challenges
  - "the treatments take time. Although the payback is longevity and QOL, at the moment the treatments can take up a large part of the day."
  - "patients feel very pressed for time."
  - "Because of the time requirement, you have to prioritise meds sometimes. Do the biggest bang for the commitment buck."
  - "The time element is the key to adherence."
  - "Therapy gets in the way of daily activities – 50 minutes two times a day!"
- Treating resistance to antibiotics is another challenge for physicians

# Positioning Bronchitol in CF Treatment

Mucus Alteration / Liquid Restoration CF Products

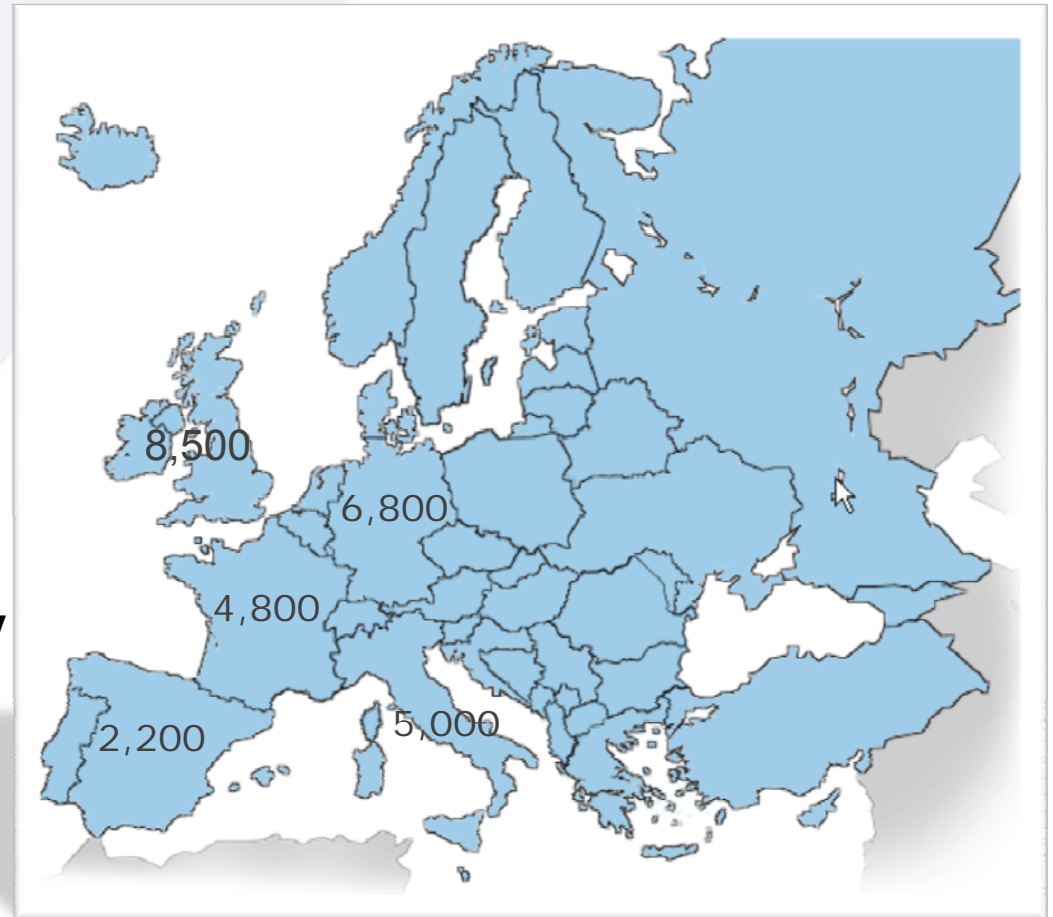
	Pulmozyme	Hypertonic Saline	Bronchitol	Denufosol	Moli1901
<b>Company</b>	Genentech	n/a	Pharmaxis	Inspire	AOP
<b>Status</b>	Market	Not registered	Phase III	Phase III	Phase II
<b>Administration</b>	Nebulizer	Nebulizer	Dry inhaler	Nebulizer	Nebulizer
<b>Dosing</b>	1x daily	2-3x daily	2x daily	3x daily	1x daily
<b>Administration Time (per total dose)</b>	20 minutes	20 minutes	<5 minutes	20 minutes	20 minutes
<b>FEV(1) Benefit</b>	6%	1%	7%	1-2%	2%

All products complimentary to anti-infective & anti-inflammatory therapies



# Bronchitol – commercialisation in EU

- **European marketing application via centralised procedure**
  - **filed October 2009**
  - **earliest approval 2H 2010**
- **Orphan drug – up to 12 years exclusivity**
- **Promotion by PXS augmented by EU partner**
- **Centralised approach to pricing**



27,000 people with CF in top 5 EU countries

# Bronchitol – cystic fibrosis registration

- **2<sup>nd</sup> Pivotal Phase III trial**



- Protocol review through Special Protocol Assessment (FDA)
- Double blind, placebo controlled, 40 centre
- 317 subjects: 6 years and older
- 400mg, twice per day for 6 months
- 1<sup>o</sup> endpoint - lung function by spirometry (FEV1)
- 2<sup>o</sup> endpoints – include antibiotic use, exacerbations, lung function



- **Enrolment closed**

**Sep 2009**

- **Headline data**

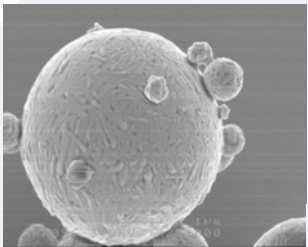
**H1 2010**

- **Orphan drug designation – U.S.**

- **Fast track designation – U.S.**



# Bronchitol - bronchiectasis



- Abnormal, irreversible dilation of the lower airways
- Daily mucus production, constant coughing, breathlessness, recurrent acute bronchitis with infective exacerbations : low quality of life
- In 30-50% of cases, the cause is unknown
- Normal lung clearance impaired
- Current treatments: bronchodilators, antibiotics
- No drugs proven effective to clear mucus

## Number of bronchiectasis patients seeking treatment

	EU	Australia	USA	Asia	Total
<b>% of patients with bronchiectasis (resp. specialists)</b>	14%	9%	N/A	5%	
<b>Trend</b>	stable or increasing	stable	increasing	stable or decreasing	
<b>Mod/Severe</b>	55%	70%	55%	75%	
<b>Patients seeking treatment</b>	210,000	18,000	110,000	250,000 ++	600,000+

Prevalence: Much higher. Bronchiectasis is often missed but has been measured as >10% of COPD patients in a US patient cohort ~ 800k

Note: US Data comes from Datamonitor research, other data from Frost & Sullivan research

# Bronchitol – bronchiectasis registration...

- **1<sup>st</sup> Pivotal Phase III trial**



- 363 patient, placebo controlled, double blind, randomised 12 week treatment (twice per day) + 12 month open label extension

- **Primary endpoints**

- quality of life – validated Patient Reported Outcome
- mucus clearance – 24hr sputum volume

- **Primary Analysis**

- quality of Life SGRQ,  $p < 0.001$  versus baseline
- SGRQ,  $p < 0.05$  versus placebo
- mucus clearance  $\uparrow 30\%$ ,  $p < 0.001$  versus placebo
- antibiotic use reduction  $p < 0.05$  versus placebo
- adverse events (52 wks) cough 9%, sore throat 5%  
no SAE attributed to treatment



# Bronchitol – bronchiectasis registration



- **2<sup>nd</sup> Phase III trial**

- ~400 patient, placebo controlled, double blind, randomised, 52 week treatment
- 400mg twice a day

- **Primary endpoint**

- Reduction in number of exacerbations

- **Secondary endpoints**

- Exercise, mucus clearance, antibiotic use
- Quality of life

- **Status**

- Special Protocol Assessment concluded with U.S. FDA
- Orphan Drug designation
- First patient enrollment
- Data

USA

October 2009

2011

# Aridol™

- Identifies airway reactivity (active airway **inflammation**) which helps physicians in the diagnosis and management of **asthma**
- An **easy-to-use test kit** provides rapid results and doesn't require specialized equipment



# International regulatory status - Aridol



- **Australia**

- First market to launch
- 75% penetration in 2 years

June 2006

- **Europe**

- Approved European Union (MRP)
- Staggered launch through distributors

May 2007



- **South Korea**

- Approved for marketing
  - Pricing approval completed (Sep 09)
  - Launched (Oct 09)

Jan 2008

- **USA**

- NDA under review
- Positive recommendation by FDA Advisory Committee
- Complete Response Letter received
- Process expected to conclude

Nov 2009

Dec 2009

1H 2010





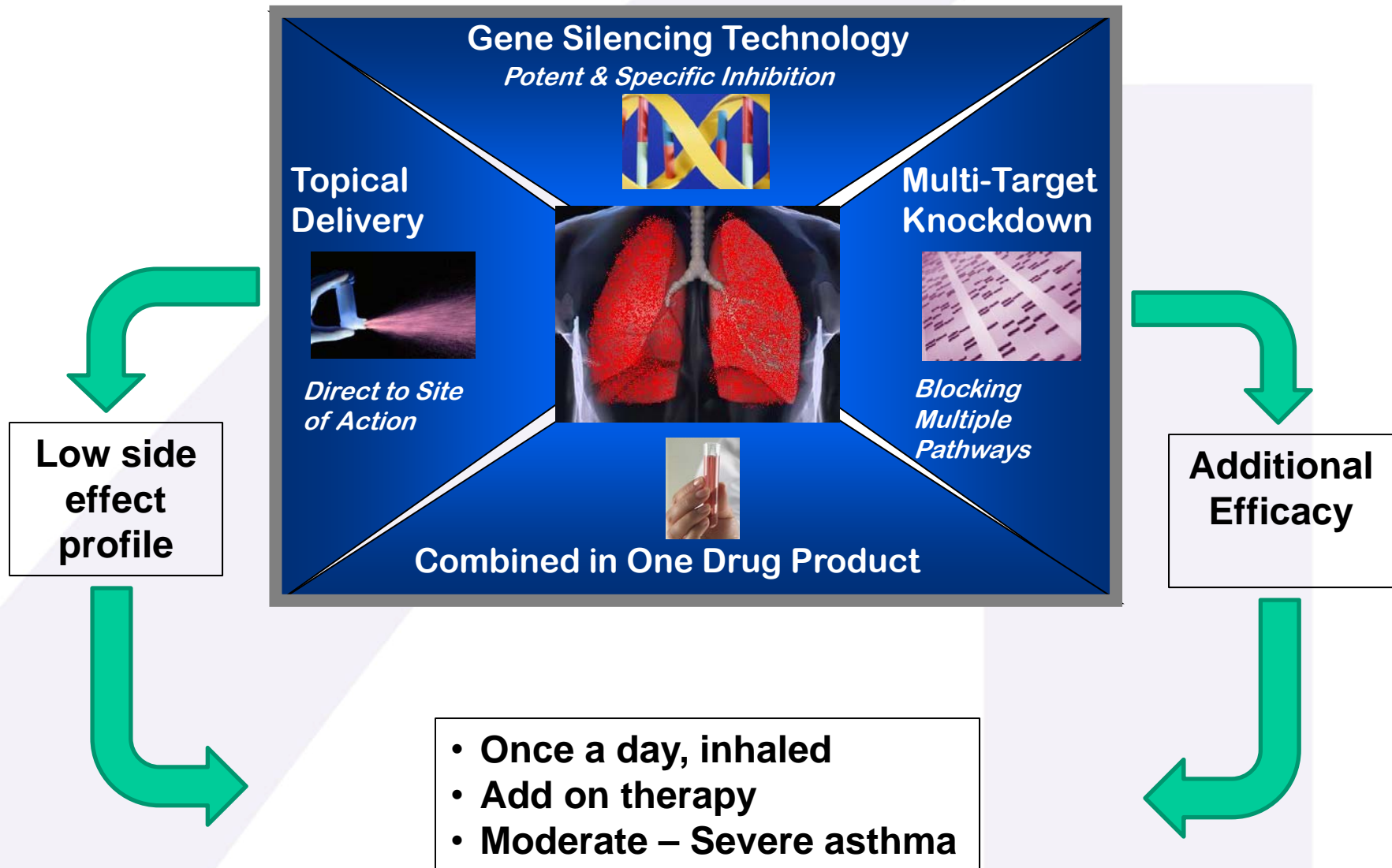
# Aridol – growth markets

	USA	KOREA	GERMANY
Existing Market size	200,000 tests p.a.	120,000 tests p.a.	660,000 tests p.a.
Pricing	+++	+	++
Market drivers	Physician reimbursement	Physician reimbursement	Physician reimbursement
	Private physician market		Private physician market
Entry route	Pharmaxis	Distributor	Distributor

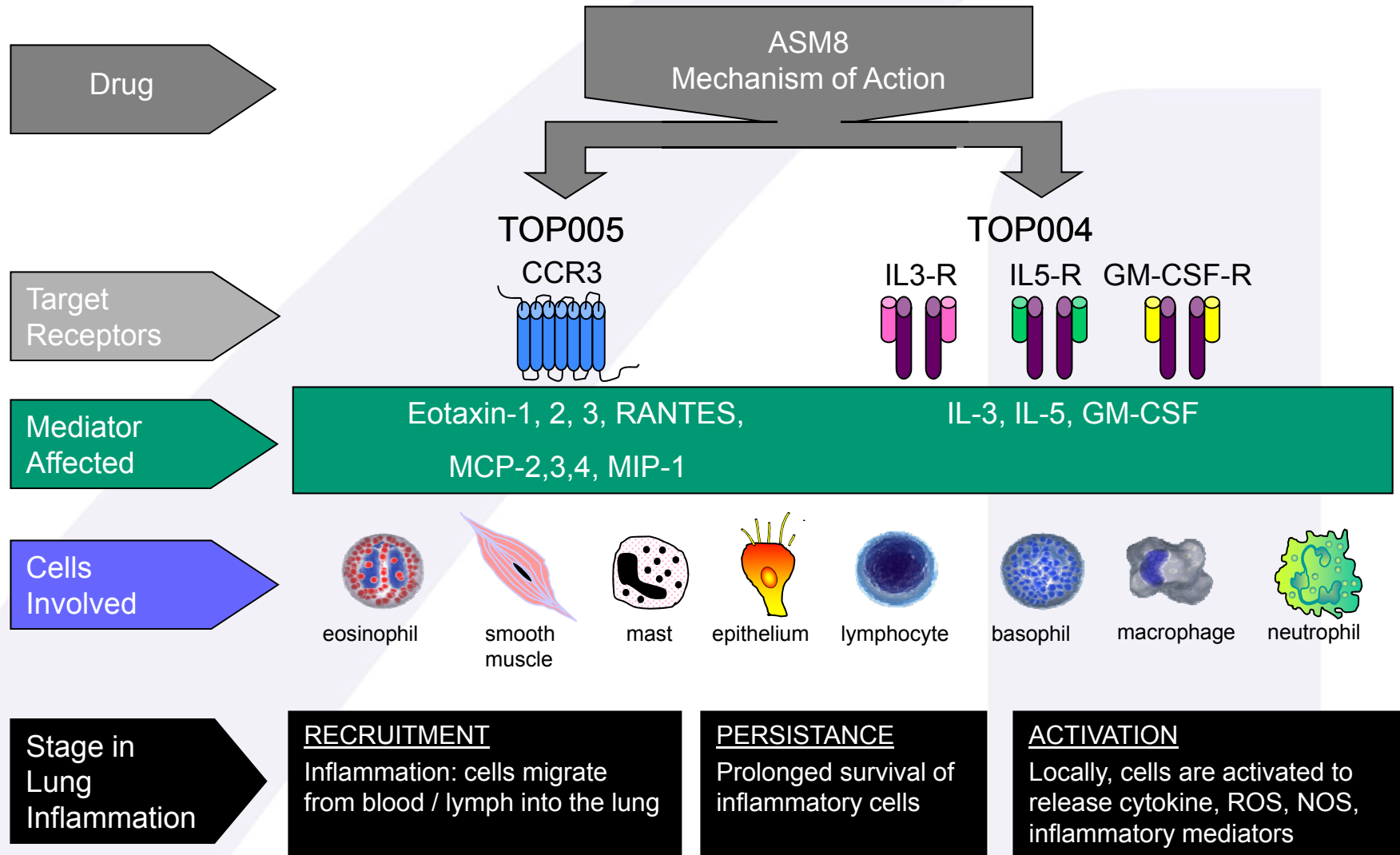
## Steroid Management

TRIAL	Data
ACRN 'BASALT' study	Q1 2009, Q1 2011
EU steroid response	Q3 2010
EU steroid titration	Q4 2010

# ASM8 : A new approach for uncontrolled asthma



# ASM8 : AON Multi-target approach against CCR3 and $\beta$ -chain



# ASM8: Clinical studies...

Phase 1 Safety	Phase 2a Allergen Challenge (4-day study)	Phase 2a Allergen Challenge (14-day study)	Phase 2a Dose Profiling
Single ascending dose comparison TPI ASM8 versus placebo (up to 6 mg)	Placebo-controlled, 4-day cross-over study (1.5 mg* Aerogen neb)	Placebo-controlled, 14-day cross-over study (1 mg* Respironics neb)	Ascending dose 1mg bd, 2mg bd, 4mg bd and 8mg od for 4 days. Allergen challenge
10 healthy subjects per dose, 5 doses	17 subjects with mild allergic asthma	18 subjects with mild allergic asthma	12 subjects with mild allergic asthma
Primary objective: <ul style="list-style-type: none"> <li>• Safety</li> </ul> Secondary objective: <ul style="list-style-type: none"> <li>• Pharmacokinetics</li> </ul>	Co-primary objectives: <ul style="list-style-type: none"> <li>• Late asthmatic resp</li> <li>• Safety</li> </ul> Secondary objectives: <ul style="list-style-type: none"> <li>• Early asthmatic resp</li> <li>• Inflammatory cells</li> <li>• Target mRNA</li> <li>• Pharmacokinetics</li> </ul> * Metered dose	Same as 4-day study in Canada  * Metered dose	Primary endpoint: <ul style="list-style-type: none"> <li>• Sputum eosinophils</li> <li>• Safety</li> </ul> Secondary objectives: <ul style="list-style-type: none"> <li>• LAR</li> <li>• EAR</li> <li>• Target mRNA</li> </ul>
complete	complete	complete	in progress

# ASM8 four day trial: results summary

## Antisense Therapy against CCR3 and the Common Beta Chain Attenuates Allergen-induced Eosinophilic Responses

Carl M. Gauvreau<sup>1</sup>, Louis Philippe Boulet<sup>2</sup>, Donald W. Cockcroft<sup>3</sup>, Adrian Bouillon<sup>4</sup>, Bharwan Chouh<sup>5</sup>, Marlene Chakrabarti<sup>6</sup>, Beth Quirk<sup>7</sup>, Tara Savelle<sup>8</sup>, Karen Hoover<sup>9</sup>, Madhav Soodani<sup>10</sup>, Richard M. Wilson<sup>11</sup>, Paolo M. Renzi<sup>12</sup>, and Paul M. O'Shea<sup>13</sup>

<sup>1</sup>Department of Medicine, McGill University, Montreal, Quebec, Canada; <sup>2</sup>Section de Cardiologie et de Pneumologie de l'Hôpital Ste-Justine, Québec, Québec, Canada; <sup>3</sup>Division of Respiratory Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada; <sup>4</sup>University of Alberta, Edmonton, Alberta, Canada; <sup>5</sup>University of Toronto, Toronto, Ontario, Canada; <sup>6</sup>University of Guelph, Guelph, Ontario, Canada; <sup>7</sup>University of Alberta, Edmonton, Alberta, Canada; <sup>8</sup>University of Alberta, Edmonton, Alberta, Canada; <sup>9</sup>University of Alberta, Edmonton, Alberta, Canada; <sup>10</sup>University of Alberta, Edmonton, Alberta, Canada; <sup>11</sup>University of Alberta, Edmonton, Alberta, Canada; <sup>12</sup>University of Alberta, Edmonton, Alberta, Canada; <sup>13</sup>University of Alberta, Edmonton, Alberta, Canada

**Abstract:** The dysregulated TPI ASM8 contains two modified phosphorothioate antisense oligonucleotides designed to inhibit allergen-induced expression of genes regulating eosinophil chemotaxis (CCR3 and the common beta chain [β<sub>2</sub>], β<sub>2</sub> L, β<sub>2</sub> H, and β<sub>2</sub> M) and granulocyte protein synthesis (argininase). This study examined the effects of inhaled TPI ASM8 on eosinophilic responses to allergen challenge in asthmatic patients. Allergic rhinitis and asthma patients with mild to moderate eosinophilic responses were randomized to receive inhaled ASM8 or placebo for 7 days. Inhaled ASM8 treatment attenuated allergen-induced eosinophilic responses, including eosinophilic infiltration of the airways, eosinophilic activation, and eosinophilic degranulation. ASM8 treatment also attenuated allergen-induced eosinophilic chemotaxis, eosinophilic activation, and eosinophilic degranulation. ASM8 treatment also attenuated allergen-induced eosinophilic chemotaxis, eosinophilic activation, and eosinophilic degranulation. ASM8 treatment also attenuated allergen-induced eosinophilic chemotaxis, eosinophilic activation, and eosinophilic degranulation. ASM8 treatment also attenuated allergen-induced eosinophilic chemotaxis, eosinophilic activation, and eosinophilic degranulation.

### AT A GLANCE COMMENTARY

**Scientific knowledge on the subject:** Inhaled oligonucleotide therapy targeting the receptors for eosinophils (CCR3) and β<sub>2</sub> L, β<sub>2</sub> H, and β<sub>2</sub> M, and granulocyte protein synthesis (argininase) using phosphorothioate modified oligonucleotides has been shown to be effective in animal models of asthma. This has not been studied in humans.

**What This Study Adds to the Field:** This study demonstrates that inhaled therapy inhibits allergen-induced eosinophilic responses in humans.

**Introduction:** TPI ASM8 attenuates the allergen-induced increase in eosinophilic chemotaxis and eosinophilic activation in asthmatic patients. Inhaled ASM8 treatment also attenuated allergen-induced eosinophilic chemotaxis, eosinophilic activation, and eosinophilic degranulation. ASM8 treatment also attenuated allergen-induced eosinophilic chemotaxis, eosinophilic activation, and eosinophilic degranulation. ASM8 treatment also attenuated allergen-induced eosinophilic chemotaxis, eosinophilic activation, and eosinophilic degranulation. ASM8 treatment also attenuated allergen-induced eosinophilic chemotaxis, eosinophilic activation, and eosinophilic degranulation.

## • ASM8 Efficacy:

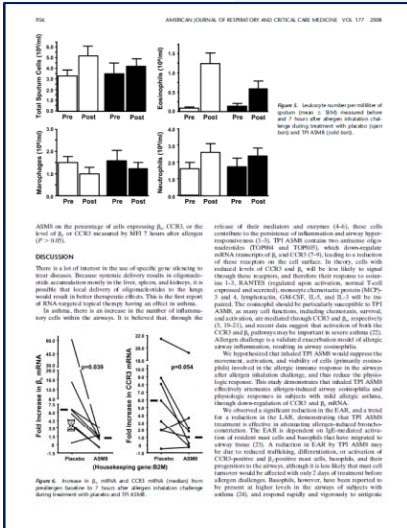
- Inhibited target genes expression
- Inhibited influx of inflammatory cell
  - Total cells, eosinophils and neutrophils
- Inhibited the EAR and the LAR after allergen challenge (1.5mg/kg)
  - Effective at low µg lung doses

## • ASM8 Safety:

- Very low systemic exposure
- Positive safety profile

## • First Clinical Study to Demonstrate:

- Efficacy in application of RNA-targeting drug in lung disease
- Validation of β<sub>2</sub>-chain and CCR3 as important targets in asthma
- Support for multi-targeted approach



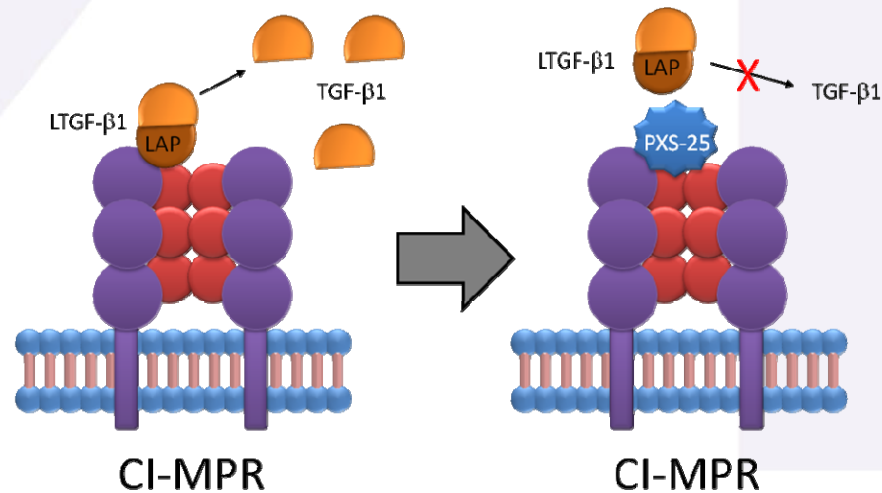
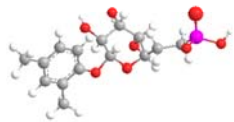
## ASM8: Dose profiling study in asthma patients



- Key trial to determine appropriate dose for future studies
- Single cohort of patients (12) receive ascending doses with two week wash-out between doses
  - Baseline
  - 1mg BD for 4 days
  - 2mg BD for 4 days
  - 4mg BD for 4 days
  - 8mg OD for 4 days
- Safety committee review including FEV<sub>1</sub> before escalating to next dose
- Measuring inflammation and lung function after allergen challenge
- Completed
- Study outcome anticipated March 2010

# PXS 25 for fibrosis

- ❑ Inhibits cleavage of latent TGF $\beta$  to active TGF $\beta$ 
  - anti-fibrotic agent with anti-inflammatory properties
  - Small molecule with robust pharmaceutical profile
  - Clinical focus is pulmonary fibrosis
- ❑ Phase I trial completed
  - Safety, pharmacokinetics in healthy subjects



# Manufacturing Capacity



- Current GMP facility
  - Manufactures Aridol for sale in EU, Asia & Australia
  - Manufacture Bronchitol for clinical trials
- New facility
  - Relocated May 2009
  - Equipment installation & validation complete
  - Complete process validation – mid 2010
  - Capacity
    - Initial capacity - 1 spray drier: 40,000 patients p.a.
    - Expanded capacity – 2nd spray drier: 80,000 patients p.a.



# Financial Statements

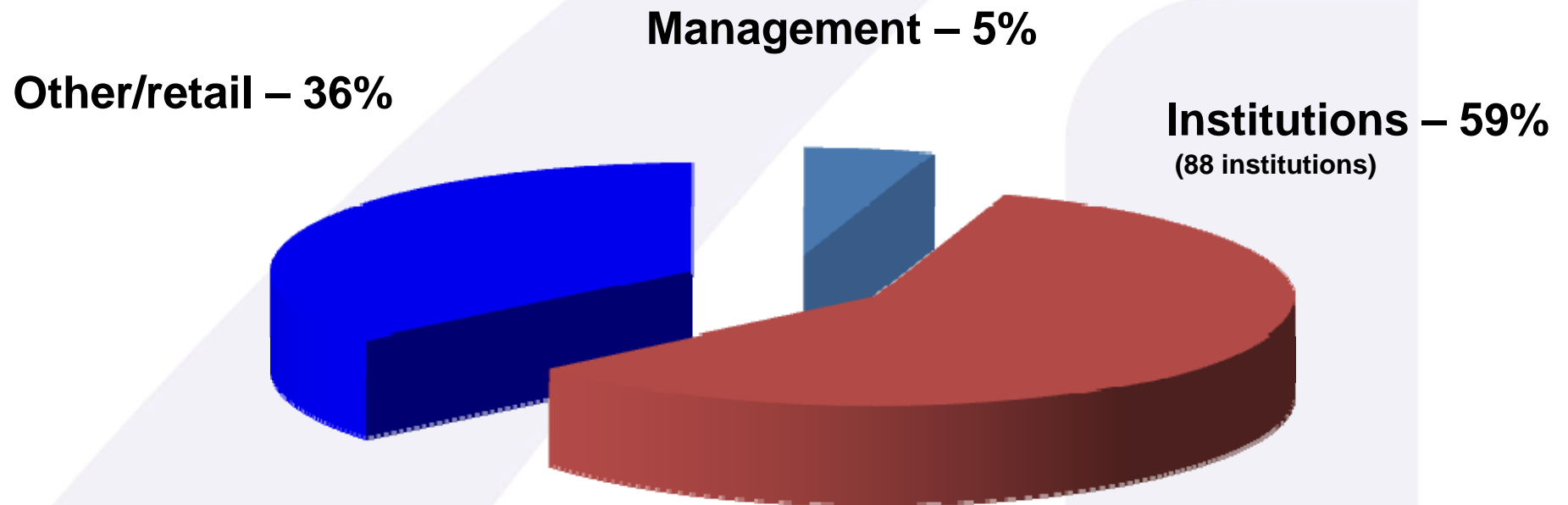
Income Statement Data	Three months ended		Six months ended	
	31-Dec-09	31-Dec-08	31-Dec-09	31-Dec-08
	A\$	A\$	A\$	A\$
Revenue from sale of goods	171	203	354	309
Cost of sales	(60)	(48)	(107)	(77)
Gross profit	111	155	247	232
Interest	978	1,581	1,930	3,657
Other income	77	141	165	144
Expenses				
Research & development	(9,184)	(7,629)	(17,295)	(13,587)
Commercial	(1,213)	(1,519)	(2,465)	(2,890)
Administration	(1,813)	(1,639)	(3,534)	(2,922)
Finance expenses	(222)	-	(508)	-
Total expenses	(12,432)	(10,784)	(23,802)	(19,399)
Loss before income tax	(11,266)	(8,907)	(21,460)	(15,366)
Income tax expense	(32)	(22)	(43)	(28)
Loss for the period	(11,298)	(8,929)	(21,503)	(15,394)
Basic and diluted earnings (loss) per share - \$	(0.052)	(0.046)	(0.099)	(0.079)
Depreciation & amortisation	641	265	1,147	518
Fair value of options issued under employee plan	549	539	1,154	1,151

# Financial Statements

Balance Sheet Data	As at			
	31-Dec-09	30-Jun-09		
	A\$	A\$		
Cash and cash equivalents	102,081	124,993		
Property, plant & equipment	32,801	32,698		
Intangible assets	1,144	1,193		
Total assets	140,634	163,997		
Total liabilities	(22,906)	(26,306)		
Net assets	117,728	137,691		
Cash Flow Data	Three months ended		Six months ended	
	31-Dec-09	31-Dec-08	31-Dec-09	31-Dec-08
	A\$	A\$	A\$	A\$
Cash flows from operating activities	(10,320)	(6,951)	(20,344)	(11,827)
Cash flows from investing activities	(909)	(4,657)	(2,233)	(6,087)
Cash flows from financing activities	(122)	-	(311)	11
Net increase (decrease) in cash held	(11,351)	(11,608)	(22,888)	(17,903)

# Share Capital

(including options)



31 December 2009: 219.1m shares; 13.5m options

END

pharmaxis