FIVE YEAR POST AUTHORISATION SAFETY STUDY OF BRONCHITOL® (INHALED MANNITOL) IN THE UK

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Introduction

- Bronchitol (inhaled dry powder mannitol) is a naturally occurring nonionic sugar alcohol that acts as an osmotic agent
- The hyperosmolarity created by Bronchitol:
  - changes the viscoelastic properties of mucus
  - increases the hydration of the periciliary fluid layer
  - contributes to increased mucus through mucociliary activity and cough provocation
- Phase III studies of Bronchitol have demonstrated early and sustained improvements in lung function (FEV_1) in patients with CF
- Bronchitol received a licence for use in adults with cystic fibrosis (CF) from the European Medicines Agency (EMA) in 2012
- Part of the licence requirement from the EMA was to perform a Post Authorisation Safety Study (PASS) using Registry data

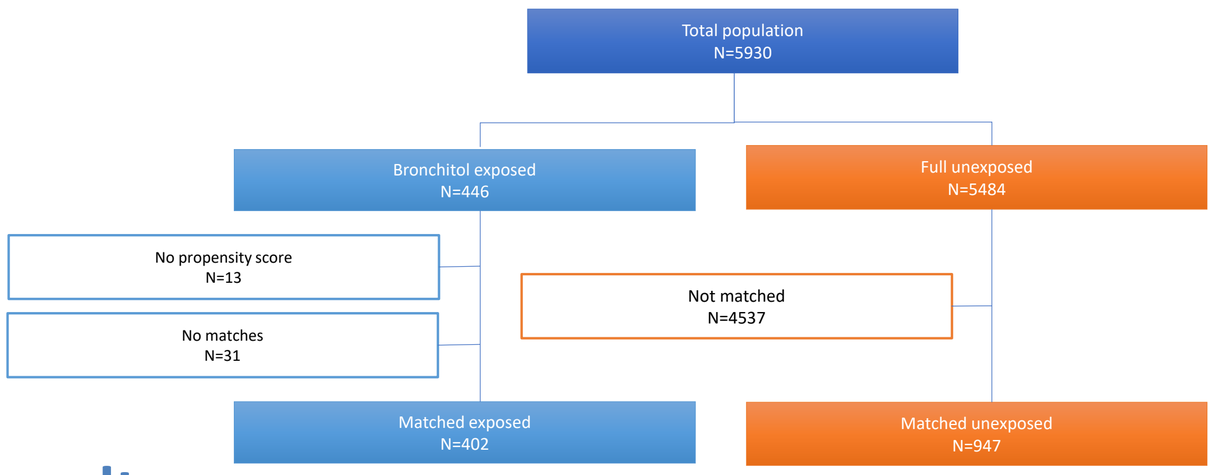
Aims

- To assess the long term safety of Bronchitol post-EMA authorisation, in a real world-setting

Methods

- All adults with one or more annual reviews in the UK CF Registry between 1st July 2010 and 31st June 2017 were included
- Propensity score matching was used with up to 3 matches chosen for each Bronchitol exposed person
- Factors in propensity score modelling were age, gender, FEV1, prior year IV antibiotic usage, chronic *Pseudomonas* and *Staphylococcus* status, presence of *Aspergillus*, treatments (dornase alpha, inhaled and oral antibiotics), BMI, asthma and haemoptysis
- Additionally, patients were matched on date of annual review

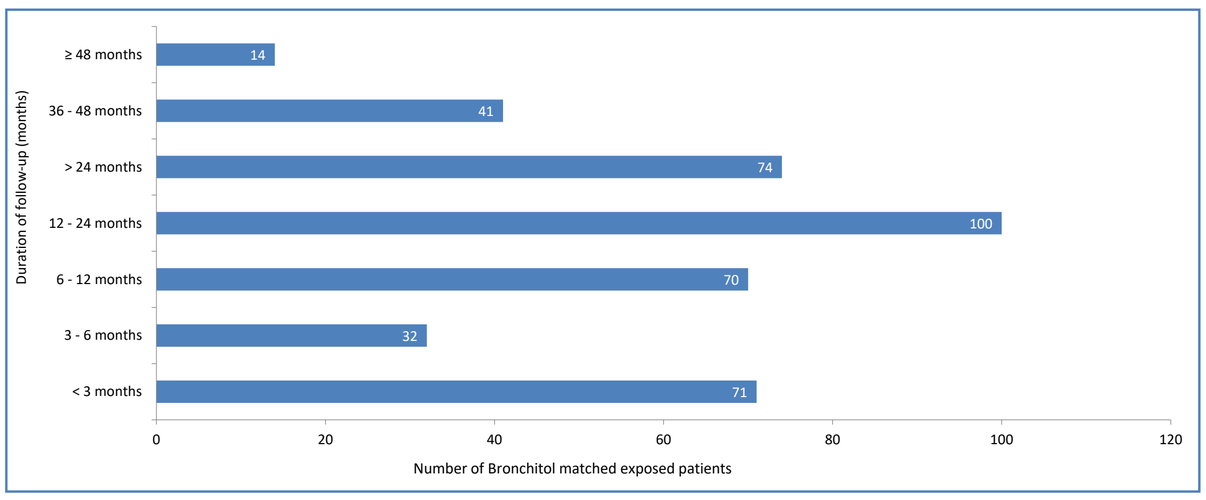
Figure 1 Propensity Matching Flow Chart



Results

- All adult patients in the UK CF Registry database with one or more annual review between 1 July 2012 and 30 June 2017 were included in the study; 446 adult patients who had a record of exposure to Bronchitol (exposed group) and 5484 adult patients with no Bronchitol exposure (full unexposed group)
- 402 exposed to Bronchitol were matched on propensity score to 947 unexposed patients (Figure 1)
- Despite matching, the exposed group had more females, lower FEV_1, lower BMI, more IV antibiotics and higher rates of haemoptysis at baseline (Table 1)
- There were no differences in the main outcome measures of haemoptysis and the cessation rate of treatment due to bronchospasm was low
- There were no reports of any of the secondary safety outcome measures of cough fracture, pulmonary abscess and septicaemia seen in the exposed group
- Median duration of exposure to Bronchitol was 15 months (Figure 2)

Figure 2 Duration of Bronchitol Use



- 131 (29.4%) stopped treatment, commonest reasons given were: cough (27), no perceived benefit (25), bronchospasm (13), non-compliance (11), death or lung transplant (7), chest tightness (5)
- There was no difference between groups in the acquisition of new infections (Tables 2a-2c)
- The annual rate of FEV_1 decline was similar in both groups at baseline and appeared to show a slight slowing overall in both groups
- Intravenous antibiotic use remained higher in the exposed group
- 25 children (<18 years) received Bronchitol "off-label"
- No safety issues were reported in this cohort

Table 1 Baseline characteristics

		Matched exposed population	Matched unexposed population	P-value
Number of patients		402	947	
Age on the index date (years)	Median	27	28	
Sex; n (%)	Male	192 (47.76)	513 (54.17)	0.031
$ppFEV_1$	Mean (SD)	59.05 (22.18)	63.60 (23.72)	<0.001
	Median	56.84	61.74	
BMI	Mean (SD)	21.77 (3.15)	22.58 (3.74)	<0.001
	Median	21.34	22.13	
Height (cm)	Mean (SD)	166.53 (8.80)	168.15 (9.50)	0.003
Weight (kg)	Mean (SD)	60.60 (11.45)	64.18 (13.39)	<0.001
	Median	58.25	62.4	
Infections Chronic Pseudomonas aeruginosa	N (%)	244 (60.7)	544 (57.44)	0.295
Chronic Staph aureus	N (%)	106 (26.37)	244 (25.77)	0.871
Positive culture for Aspergillus at baseline	N (%)	91 (22.64)	181 (19.11)	0.161
Previous complications History of haemoptysis at the last annual review prior to the index date *	N (%)	37 (9.20)	53 (5.60)	0.021
Days on IV antibiotics at previous annual review	Mean (SD)	31.14 (34.12)	23.97 (33.45)	0.0004

Summary statistics are derived from patients with available data

Table 2a. Acquisition of new *Staphylococcus aureus*

	New Staph aureus	No new Staph aureus	Odds Ratio(95% CI)	Adjusted odds ratio (95% CI)
Matched exposed (n=255)	55	200	0.78 (0.55, 1.11)	0.78 (0.54, 1.13) p=0.187
Matched unexposed (n=601)	156	445		

Table 2b. Acquisition of new *Pseudomonas aeruginosa*

	New Pseudomonas	No new Pseudomonas	Odds Ratio (95% CI)	Adjusted odds ratio (95% CI)
Matched exposed (n=134)	40	94	0.94 (0.61, 1.46)	0.67 (0.42,1.09) p=0.105
Matched unexposed (n=341)	106	235		

Table 2c. Acquisition of new *Aspergillus* species

	New Aspergillus	No new Aspergillus	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Matched exposed (n=299)	62	237	1.40 (0.99, 1.98)	1.36 (0.94, 1.97) p=0.101
Matched unexposed (n=693)	109	584		

Analysed using logistic regression. Models adjust for age at baseline, duration of follow-up, sex, baseline FEV_1, baseline BMI,, asthma at baseline, treatments: DNase, inhaled antibiotics, long-term antibiotics. In each model the infection being tested for was not present at baseline. In Table 2c the model included adjustment for number of samples and type of sample (only sputum and BAL samples)
Only those without the infections at baseline are included in these analyses

Conclusions

- This 5-year real-world study complements the extensive safety data from a broad clinical trial program
- The types of complications reported among the exposed and matched unexposed patient groups in this study reflect the underlying CF disease state
- The most common complications reported during the study in the matched-exposed group were: CF-related diabetes, osteopenia, GERD, elevated liver enzymes, sinus disease, arthropathy, liver disease, ABPA and asthma
- These were also the most commonly reported complications in the matched unexposed group and the full unexposed group.
- This study confirmed there was no increase in haemoptysis in the Bronchitol-exposed population
- There were no differences in other safety outcomes, including the rate of acquisition of new infections
- The benefit-risk of Bronchitol for use in CF patients is unchanged and remains positive with no new emergent safety signals identified during this 5-year observational safety study.

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