

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 (FEV₁) 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

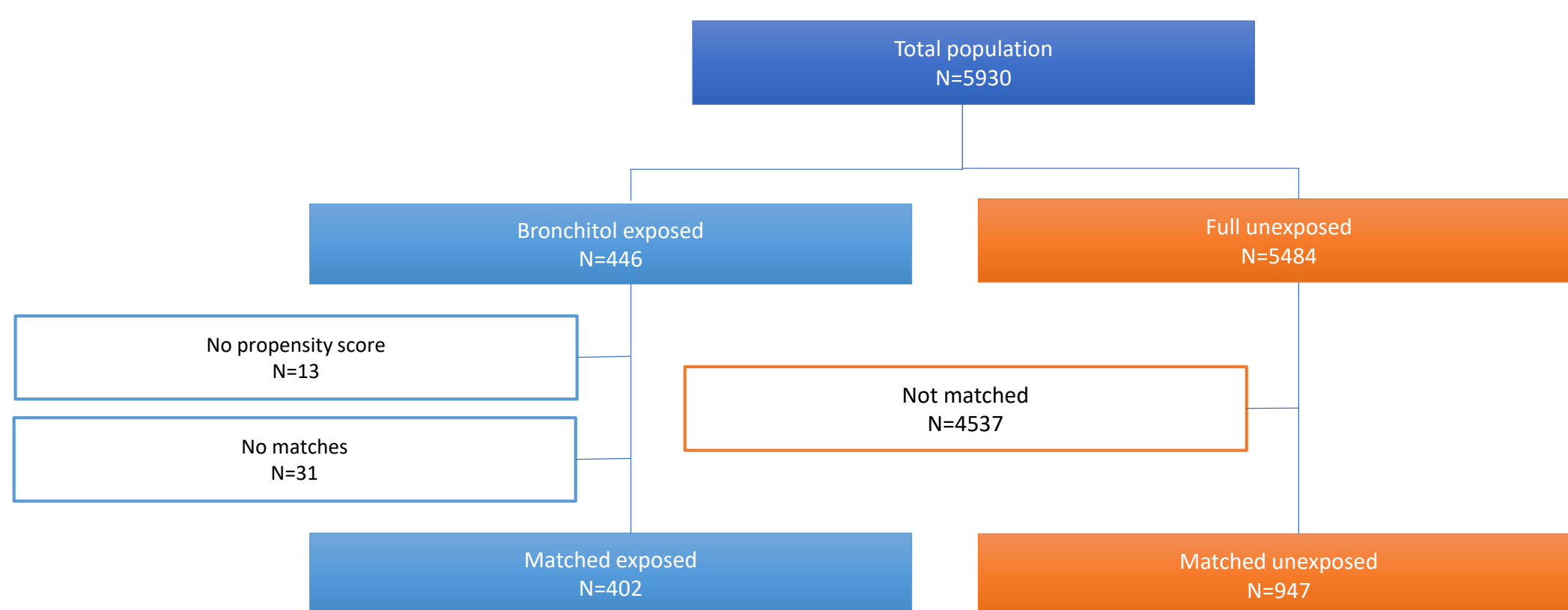
Aims

- 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

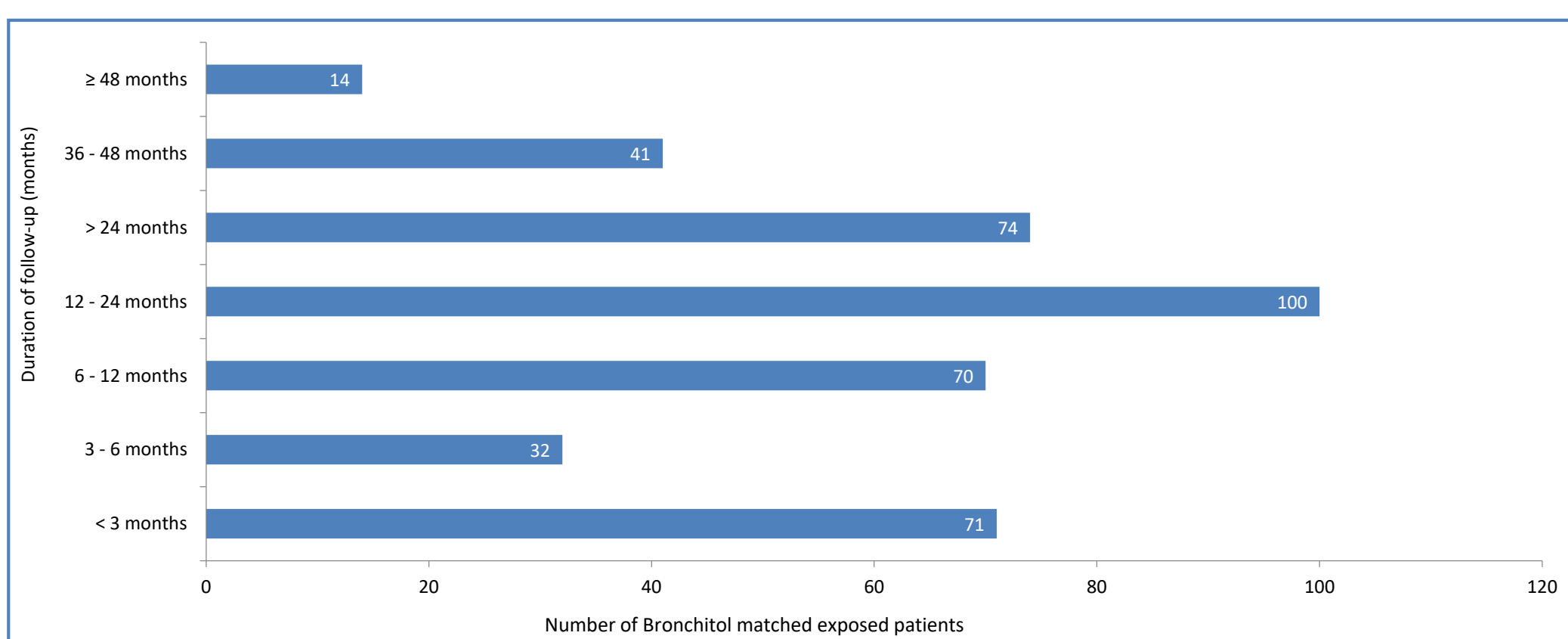
Figure 1 Propensity Matching Flow Chart



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 FEV₁, 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 FEV₁ 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) Median 56.84	63.60 (23.72) 61.74	<0.001
BMI	Mean (SD) 21.77 (3.15) Median 21.34	22.58 (3.74) 22.13	<0.001
Height (cm)	Mean (SD) 166.53 (8.80)	168.15 (9.50)	0.003
Weight (kg)	Mean (SD) 60.60 (11.45) Median 58.25	64.18 (13.39) 62.4	<0.001
Infections			
Chronic <i>Pseudomonas aeruginosa</i>	N (%) 244 (60.7)	544 (57.44)	0.295
Chronic <i>Staph aureus</i>	N (%) 106 (26.37)	244 (25.77)	0.871
Positive culture for <i>Aspergillus</i> 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 <i>Staph aureus</i>	No new <i>Staph aureus</i>	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 <i>Pseudomonas</i>	No new <i>Pseudomonas</i>	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 <i>Aspergillus</i>	No new <i>Aspergillus</i>	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 FEV₁, 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.