BRONCHITOL FOR MANAGEMENT OF CYSTIC FIBROSIS IN ADULT PATIENTS

SPONSOR BRIEFING DOCUMENT

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACT	Airway Clearance Therapy
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ATS/ERS	American Thoracic Society/European Respiratory Society
AUC	Area Under the Plasma Concentration versus Time Curve
BID	Twice Daily
BMI	Body Mass Index
BOCF	Baseline Observation Carried Forward
CF	Cystic Fibrosis
CFF	Cystic Fibrosis Foundation
CFQ-R	Cystic Fibrosis Questionnaire Revised
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CI	Confidence Interval
C_{max}	Maximum Observed Plasma Concentration
CRL	Complete Response Letter
DPI	Dry Powder Inhaler
EEA	European Economic Area
FDA	Food and Drug Administration
FEF_{25-75}	Forced Expiratory Flow in Middle Half of an Expiration
FEV_1	Forced Expiratory Volume in First Second of Expiration
FVC	Forced Vital Capacity
GRAS	Generally Recognized as Safe
ITT	Intent-to-Treat
IUDR	Imputation Using Drop-Out Reason
IV	Intravenous
MMRM	Mixed Model Repeated Measures
MTT	Mannitol Tolerance Test
NDA	New Drug Application
PADAC	Pulmonary-Allergy Drugs Advisory Committee
PDPE	Protocol Defined Pulmonary Exacerbation
PK	Pharmacokinetic
PT	Preferred Term
rhDNase	Recombinant Human Deoxyribonuclease
SAE	Serious Adverse Event
T_{max}	Time to Peak Plasma Concentration
UK	United Kingdom
US	United States
WHO	World Health Organization

1 EXECUTIVE SUMMARY

Chiesi USA, Inc. (Chiesi) is seeking approval of Bronchitol, an inhaled dry powder form of mannitol, for the management of cystic fibrosis (CF) to improve pulmonary function in patients 18 years and older in conjunction with standard therapies. Mannitol is a naturally occurring sugar alcohol found in most vegetables and is used extensively as a food additive. Once inhaled, Bronchitol creates an osmotic gradient that draws water into the airway lumen, enhancing the clearance of mucus via ciliary action and cough. Bronchitol is dosed at 400 mg twice daily (BID) and is administered by a portable, easy-to-use dry powder inhaler (DPI).

This briefing document presents data from the Bronchitol New Drug Application (NDA) re-submission, which support the efficacy and safety of Bronchitol in adult patients with CF. The primary evidence of the positive benefit-risk profile of Bronchitol in adults comes from three similar randomized, double-blind controlled Phase 3 studies.

Bronchitol consistently demonstrated definitive, clinically meaningful improvements in lung function, as measured by FEV_1, has an acceptable safety profile, and is generally well-tolerated based on the clinical trials and 8 years of world-wide clinical experience.

1.1 Background and Unmet Need

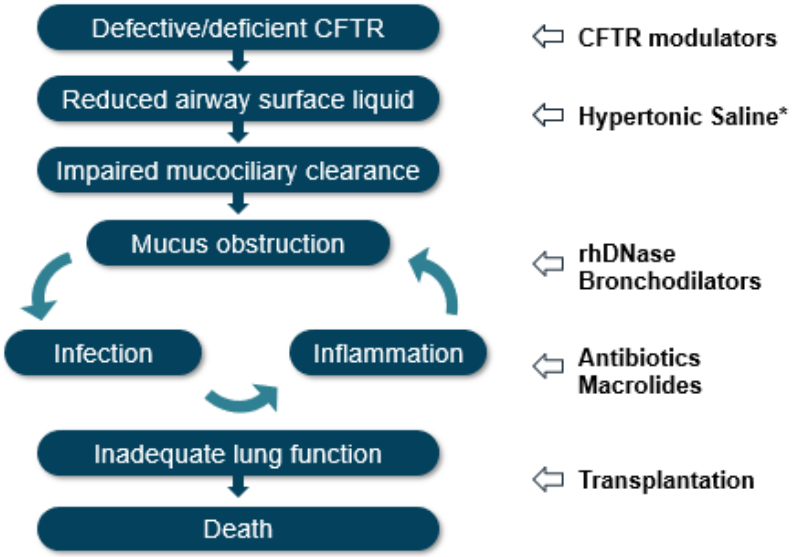
Cystic fibrosis is a progressive, life-shortening, genetic disease caused by autosomal recessive mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Cystic fibrosis is mostly diagnosed by newborn screening and occurs in approximately 30,000 patients and more than 800 new patients per year in the United States (US) (Cystic Fibrosis Foundation [CFF] Registry 2017). The majority (>90%) of patients with CF are Caucasian, and the disease occurs equally in males and females. The estimated median life expectancy is approximately 44 years in the US, and the number of adult patients continues to increase (CFF Registry 2017).

While CF is a multi-organ disease, the greatest impact is on the lungs, which is consequently the target organ for most therapeutic interventions. The genetic defect in the CFTR causes dehydration of the airway surface liquid layer and reduction in mucociliary clearance from the lungs, which leads to accumulation of thick, sticky mucus; chronic bronchopulmonary infection; and impaired lung function. Cystic fibrosis is characterized by a progressive decline in lung function over the patient's lifetime and chronic inflammation in the pulmonary tissues. The cycle of chronic obstruction, infection, and inflammation ultimately contributes to the occurrence of respiratory failure, which accounts for more than 80% of mortality in patients with CF (Flume 2012).

Within the context of CF pulmonary disease, lung function is the most prominent measure of disease severity, progression, and therapeutic efficacy. Pulmonary function is commonly measured by FEV_1, which is the maximal amount of air that can be forcefully exhaled in one second. FEV_1 is the strongest clinical predictor of survival among patients with CF (Szczesniak 2017) and is therefore a key endpoint for determination of efficacy of treatment modalities in CF clinical studies (Liou 2010, Mayer-Hamblett 2007, VanDevanter 2012).

A crucial goal of CF therapy is to improve lung function and delay the resultant respiratory failure. Treatment approaches for CF focus on different steps of the pathophysiological pathway of lung disease including targeting the genetic defect, improving mucociliary clearance, suppressing the growth of bacterial pathogens, and attenuating airway inflammation. Consequently, patients must be treated with multiple therapies in an effort to enhance lung function or mitigate its inexorable decline (Figure 1). No single treatment is sufficiently effective as monotherapy to optimize treatment response in terms of lung function.

Figure 1: Cystic Fibrosis Pathophysiological Pathway and Recommended Therapies



*Hypertonic saline is not approved in the US for treatment of cystic fibrosis.
CFTR=Cystic Fibrosis Transmembrane Conductance Regulator; rhDNase=Recombinant human deoxyribonuclease

Despite the introduction of CFTR modulators for patient groups with specific gene mutations, most patients still require mucoactive agents and additional therapeutics that target downstream manifestations of the disease. Mucoactive treatments including recombinant human deoxyribonuclease (rhDNase) and hypertonic saline, as well as bronchodilators, inhaled antibiotics, and macrolides, work lower in the CF cascade than CFTR modulators. While rhDNase is effective at reducing mucus viscosity, it has not been shown to significantly improve mucociliary clearance (Robinson 2000). Hypertonic saline is often used to try to achieve this goal by hydrating the mucus layer, but it is not approved by the Food and Drug Administration (FDA) for the treatment of CF and can be difficult to tolerate at high concentrations (Robinson 1997).

Additional limitations of hypertonic saline and rhDNase include the time required for setup, drug administration, and cleaning of the nebulizer and the potential risk of infection. Patients are reported to spend up to 40 minutes per day using nebulizers in a BID regimen which significantly adds to the patient's daily treatment burden (Sawicki 2009). Possible microbial contamination of nebulizers may also be a source of airway infection or reinfection in patients with CF (Blau 2007).

A medical need exists for a convenient, easy-to-use, safe treatment that improves airway mucus clearance, in conjunction with standard therapies. There is currently no approved therapy that targets mucociliary clearance impairment in patients with CF to improve their pulmonary function.

1.2 Product Description

Bronchitol is an inhaled hyperosmotic agent designed to increase mucus clearance and thereby improve lung function in patients with CF. Bronchitol consists of two components: the drug product, which is a spray dried mannitol powder in capsules, and a DPI. The proposed dose of Bronchitol is 400 mg of dry powder mannitol, which is to be administered by oral inhalation of ten 40 mg hard gelatin capsules BID using the DPI.

The Bronchitol DPI is a simple, easy-to-use, manually operated dry powder delivery system (Figure 2). The total inhalation process typically takes 5 minutes to complete. Each inhaler is used for one week and discarded, and therefore does not require cleaning and maintenance.

Figure 2: Bronchitol Capsules and Dry Powder Inhaler

Mannitol is classified by the FDA as a Generally Recognized as Safe (GRAS) excipient for food substances and is used as a pharmaceutical excipient in many products (Rowe 2009). Overall, systemic mannitol exposure resulting from food consumption is significantly greater than that from exposure with Bronchitol and provides extensive systemic safety experience.

1.2.1 Mechanism of Action

Bronchitol is a hyperosmotic agent which increases the hydration of the airway surface liquid leading to a change in the viscoelastic properties of mucus, and in turn to increased mucociliary and cough clearance of mucus, which is impaired in patients with CF (Daviskas 2005, Robinson 1999).

1.2.2 Global Marketing Approvals

Bronchitol was first approved in 2011 in Australia. As of December 2018, the drug has been approved in 35 countries for the management of CF in adult patients and is currently marketed in 8 countries, with approximately 8,000 patients treated.

1.3 Clinical Development Program

1.3.1 United States Regulatory History

An NDA for Bronchitol was submitted in 2012 for the management of CF in patients aged 6 years and older to improve pulmonary function, based on results from two Phase 3 studies (Study 301 and Study 302) completed in 2010. In the original application, the population included pediatric and adult patients. The treatment differences in favor of Bronchitol compared to control were observed for the primary endpoint of change in FEV_1 from baseline over 26 weeks (0.083 L in Study 301 [p<0.001] and 0.054 L in Study 302 [p=0.059]).

In January 2013, the Pulmonary-Allergy Drug Advisory Committee (PADAC) reviewed the data and discussed the impact of missing data on the primary endpoint and nonsignificant primary endpoint results in Study 302. In addition, safety concerns were raised in relation to the pediatric population.

Following the PADAC meeting, the FDA issued a Complete Response Letter (CRL), stating that Study 301 and 302 did not provide a favorable benefit-risk balance to support the use of Bronchitol in patients with CF 6 years of age and older. The FDA recommended conducting an additional adequate clinical study to show evidence of efficacy in adult patients and to confirm an acceptable safety profile. The sponsor was encouraged to include pre-specified criteria that address the specific safety concern of hemoptysis and use adult data to inform the potential for further evaluation of the product in the pediatric population.

In the subsequent End of Review meeting, the FDA stated that the clearest and most expedient regulatory path forward for the Bronchitol program would be to conduct a third study to establish the efficacy of Bronchitol in patients with CF. It was recommended that the study be similar to the previous two studies in terms of design, duration, and comparator and should include proactive steps to minimize patient dropouts. The FDA also strongly recommended that the study be performed in adults only (18 years of age).

Based on these discussions with the FDA, Study 303 was conducted in adult patients with CF and completed in 2017. In the NDA pre-submission meeting, presentation of data and statistical analyses were discussed and agreed upon, including focusing on the adult population and re-analyzing earlier studies using methods from Study 303. The Statistical Analysis Plan for Study 303 was reviewed by the FDA.

The Bronchitol NDA was resubmitted in December 2018 for management of CF in patients 18 years and older.

1.3.2 Clinical Program

The Bronchitol clinical program consists of nine clinical studies, and the primary safety and efficacy data are derived from adult patients in the three Phase 3 studies – Studies 301, 302, and 303. These studies include a total of 789 randomized adult patients.

1.4 Efficacy Findings

1.4.1 Study Design

Studies 301, 302, and 303 were Phase 3 randomized, double-blind, controlled studies with similar study designs. Study 303 enrolled adult patients with CF with mild-to-severe lung function impairment, assessed by percent predicted FEV_1. Studies 301 and 302 enrolled both adult and pediatric patients (aged 6-17 years). The pediatric age group is not included in the proposed target population and therefore data from these patients are not presented in this briefing document.

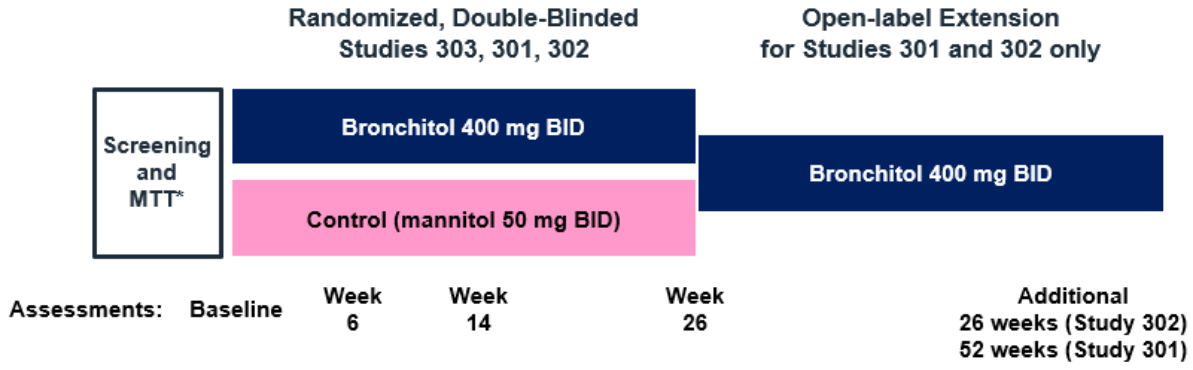
Each of the three Phase 3 studies included a 26-week double-blind treatment phase, during which patients were randomized to either Bronchitol 400 mg BID or control (Figure 3). As discussed with the FDA, a low dose of inhaled mannitol (50 mg) BID was used as the control because it provided the same taste and appearance as Bronchitol, thus ensuring effective blinding of the studies.

At the initial screening, eligible patients were evaluated for bronchial hyperresponsiveness to inhaled mannitol using the mannitol tolerance test (MTT), which was conducted under medical supervision.

Following randomization, evaluations were conducted at Weeks 6, 14, and 26 of the double-blind treatment phase, including spirometry assessments.

Following the 26-week double-blind phase, Studies 301 and 302 had open-label extension phases. Study 301 included two 26-week open-label extensions (total of 52 weeks) and Study 302 had one 26-week open-label extension phase.

Figure 3: Phase 3 Study Design



*Mannitol Tolerance Test (MTT) administered under medical supervision
BID=Twice Daily

Endpoints

The primary endpoint in each study was the change from baseline in FEV_1 (L) over 26 weeks.

Pulmonary function secondary endpoints included in each study were change from baseline in forced vital capacity (FVC) over 26 weeks and change from baseline in forced expiratory flow during the mid-portion of the FVC (FEF_{25-75}) over 26 weeks.

The rate of protocol-defined pulmonary exacerbation (PDPE; defined in Section 6.1.4.2) and change in symptoms using the Cystic Fibrosis Questionnaire Revised (CFQ-R) respiratory domain were also included as secondary endpoints. Additional secondary endpoints are described in Section 6.1.5.2.

Statistical Analyses

In Study 303, the Intent-to-Treat (ITT) Set was defined as all patients randomized. The primary endpoint was assessed using Mixed Model Repeated Measures (MMRM), and implemented an imputation using drop-out reason (IUDR) approach. Missing post-baseline data due to withdrawal from the study caused by an adverse event (AE), physician decision, or lack of efficacy were imputed using a baseline observation carried forward (BOCF) single imputation method, while missing data for other reasons were not imputed. A set of sensitivity analyses were pre-planned in order to evaluate the robustness of study results under different assumptions. The Statistical Analysis Plan for Study 303 was shared and reviewed by the FDA.

To permit a comparison of results between studies, the same statistical methods and analysis population used for Study 303 were also applied to Studies 301 and 302 (adult patients) and to the integrated analysis of the three Phase 3 studies. Results for Studies 301 and 302 in the adult population are presented with 95% confidence intervals (CIs) and p-values, with the acknowledgement that these analyses were performed post hoc.

1.4.2 Efficacy Results

In Study 303, a total of 486 patients were MTT screened, and 454 (93.4%) passed the MTT. Of these, 423 patients were randomized and 420 were treated. Most patients completed the 26-week double-blind treatment in both the Bronchitol (87.6%) and control (88.8%) groups (Table 1).

In the three Phase 3 studies, 896 adult patients underwent the MTT, and 824 patients (92.0%) successfully completed the test. Overall, 789 adult patients (88.1%) were randomized to treatment with either Bronchitol 400 mg BID or control across the three Phase 3 studies.

A total of 616 patients (78.1%) completed the 26-week double-blind treatment. The primary reasons for discontinuing the study were withdrawal of consent and AEs.

Table 1: Summary of Patient Disposition in Phase 3 Studies (≥18 Years)

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	**Bronchitol N=124**	**Control N=85**	**Bronchitol N=97**	**Control N=60**	**Bronchitol N=430**	**Control N=359**
Randomized (ITT Set), n (%)	209 (100.0)	214 (100.0)	124 (100.0)	85 (100.0)	97 (100.0)	60 (100.0)	430 (100.0)	359 (100.0)
Treated (Safety Set), n (%)	207 (99.0)	213 (99.5)	114 (91.9)	76 (89.4)	93 (95.9)	58 (96.7)	414 (96.3)	347 (96.7)
Completed the DBP, n (%) [a]	183 (87.6)	190 (88.8)	71 (57.3)	52 (61.2)	70(72.2)	50 (83.3)	324 (75.3)	292 (81.3)
Prematurely withdrawn from study, n (%)	26 (12.4)	24 (11.2)	53 (42.7)	33 (38.8)	27 (27.8)	10 (16.7)	106 (24.7)	67 (18.7)
Primary Reason for Study Withdrawal, n (%)								
Consent withdrawal	12 (5.7)	13 (6.1)	18 (14.5)	17 (20.0)	10 (10.3)	6 (10.0)	40 (9.3)	36 (10.0)
Adverse event	10 (4.8)	6 (2.8)	24 (19.4)	12 (14.1)	9 (9.3)	2 (3.3)	43 (10.0)	20 (5.6)
Physician decision	0	0	5 (4.0)	1 (1.2)	2 (2.1)	1 (1.7)	7 (1.6)	2 (0.6)
Sponsor decision	0	0	5 (4.0)	2 (2.4)	0	0	5 (1.2)	2 (0.6)
Lost to follow-up	1 (0.5)	1 (0.5)	0	0	2 (2.1)	0	3 (0.7)	1 (0.3)
Lack of efficacy	2 (1.0)	1 (0.5)	0	0	0	0	2 (0.5)	1 (0.3)
Other	1 (0.5)	3 (1.4)	1 (0.8)	1 (1.2)	4 (4.1)	1 (1.7)	6 (1.4)	5 (1.4)

a In Study 303 patients who discontinued study medication could remain in the study.
ITT set: all patients randomized.
DBP=Double-blind phase; ITT=Intent-to-treat.

The patients enrolled in the three studies had similar demographics (Table 2) and were representative of the patient population with CF in the US (CFF Registry 2017). The mean age of patients was approximately 28 years, and the majority of patients were male and white. The average body mass index (BMI) was about 22 kg/m^2, and approximately 27% of patients were within the US.

Disease characteristics in the adult patients were generally similar for all three Phase 3 studies. The mean percent predicted FEV_1 at screening was approximately 61%. In Study 303, 44.0% of the patients in Study 303 had *Pseudomonas aeruginosa* infections present in sputum at time of screening compared to 60.9% of patients in Studies 301 and 302 who had positive pseudomonas cultures.

The majority (61.0%) of patients in Study 303 and 302 did not experience a pulmonary exacerbation requiring hospitalization in the previous year.

Importantly, patient access to, and use of, therapies to treat CF was similar across the three studies, with most patients treated with rhDNase (64.0% and 64.9% in the Bronchitol and control groups, respectively).

Table 2: Summary of Patient Demographics and Baseline Characteristics in Phase 3 Studies (≥18 Years)

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	**Bronchitol N=124**	**Control N=85**	**Bronchitol N=97**	**Control N=60**	**Bronchitol N=430**	**Control N=359**
Mean Age[a], years (SD)	26.8 (7.64)	28.6 (10.75)	29.3 (9.24)	29.0 (8.69)	27.0 (7.88)	28.8 (8.50)	27.6 (8.24)	28.7 (9.92)
Male (%)	117 (56.0)	107 (50.0)	73 (58.9)	39 (45.9)	59 (60.8)	37 (61.7)	249 (57.9)	183 (51.0)
Race, n (%)								
White	202 (96.7)	209 (97.7)	121 (97.6)	84 (98.8)	96 (99.0)	60 (100.0)	419 (97.4)	353 (98.3)
Other	7 (3.3)	5 (2.3)	3 (2.4)	1 (1.2)	1 (1.0)	0	11 (2.6)	6 (1.7)
Geographic Region								
US	57 (27.3)	59 (27.6)	0 (0)	0 (0)	57 (58.8)	36 (60.0)	114 (26.5)	95 (26.5)
Non-US	152 (72.7)	155 (72.4)	124 (100)	85 (100)	40 (41.2)	24 (40.0)	316 (73.5)	264 (73.5)
Mean BMI[a] kg/m^2 (SD)	22.12 (3.79) [b]	22.30 (4.13)	22.85 (3.48)	22.06 (3.52)	22.33 (3.91)	22.45 (3.19)	22.38 (3.74) [c]	22.27 (3.84)
Disease Severity (FEV_1 % of Predicted Normal Value at Baseline)								
Mean (SD)	63.17 (15.15)	62.98 (13.65)	57.95 (15.76)	58.46 (16.98)	61.48 (15.23)	60.34 (14.47)	61.28 (15.47)	61.47 (14.72)
Disease Severity (% Predicted FEV_1 at Baseline), n (%)								
≤ 50%	51 (24.4)	46 (21.5)	39 (31.5)	29 (34.1)	23 (23.7)	21 (35.0)	113 (26.3)	96 (26.76)
> 50% to ≤70%	82 (39.2)	102 (47.7)	53 (42.7)	29 (34.1)	43 (44.3)	21 (35.0)	178 (41.4)	152 (42.3)
> 70%	76 (36.4)	66 (30.8)	32 (25.8)	27 (31.8)	31 (32.0)	18 (30.0)	139 (32.3)	111 (30.9)
Presence of *Pseudomonas aeruginosa* at screening[a], n (%)								
n (%)	93 (44.5)	93 (43.5)	75 (60.5)	57 (67.1)	57 (58.8)	34 (56.7)	225 (52.3)	184 (51.3)
Pulmonary Exacerbation Hospitalization in 12 Months Before Screening, n (%)								
0	121 (57.9)	135 (63.1)	-	-	59 (60.8)	39 (65.0)	-	-
1	57 (27.3)	43 (20.1)	-	-	20 (20.6)	16 (26.7)	-	-
≥2	31 (14.8)	36 (16.8)	-	-	18 (18.6)	5 (8.3)	-	-
Use of rhDNase [a], n (%)	144 (68.9)	142 (66.4)	64 (51.6)	49 (57.6)	67 (69.1)	42 (70.0)	275 (64.0)	233 (64.9)

a At screening; b n=208.c n=429.

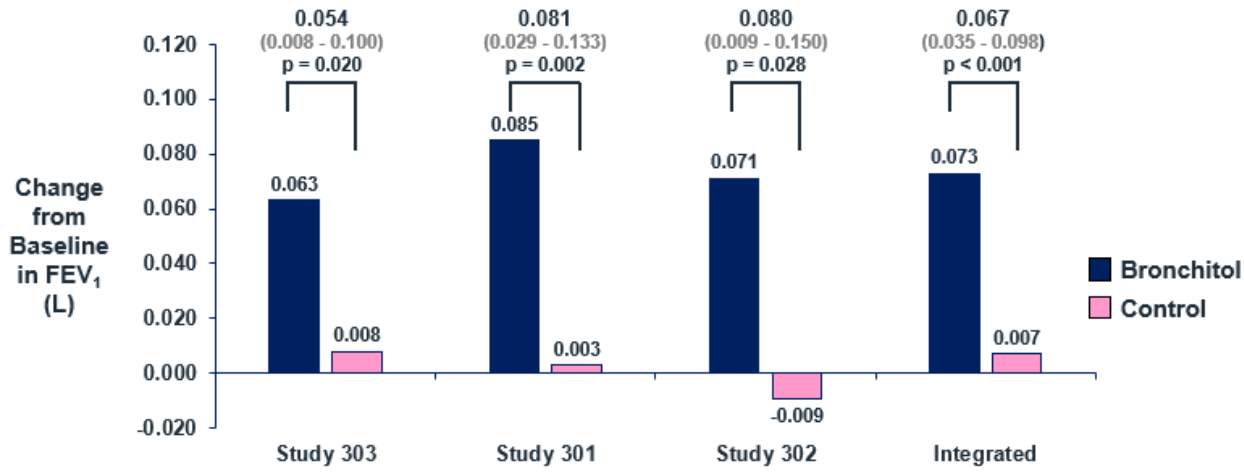
BMI=Body mass index; FEV_1=Forced expiratory volume in 1 second; SD=Standard deviation

1.4.2.1 FEV$_1$ Primary Efficacy Results and Sensitivity Analyses

In Study 303, the difference between treatments was statistically significant in favor of Bronchitol compared to control with an adjusted mean difference (95% CI) of 0.054 L (0.008; 0.100), p=0.020 (Figure 4).

When identical statistical methods were applied to Study 301 and 302 (adult population), improvements in FEV_1 over the 26-week treatment period in favor of Bronchitol were also observed.

Figure 4: Change from Baseline in FEV_1 over the 26-week Treatment Period (≥18 Years, ITT Set)

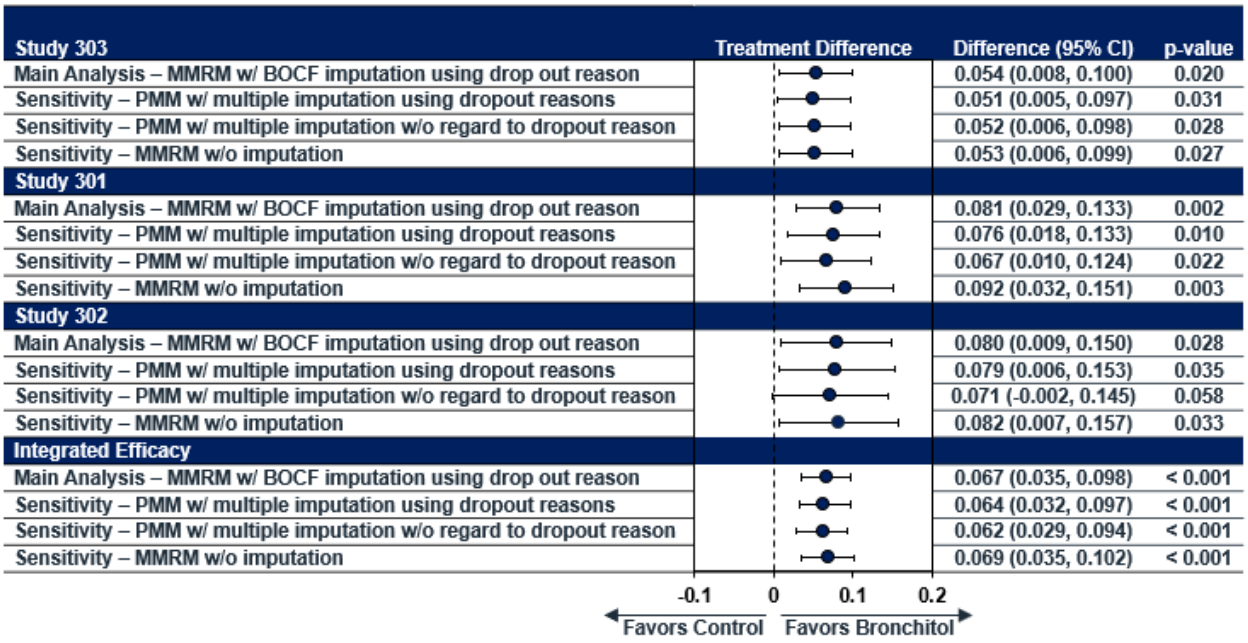


Mixed Model Repeated Measures with baseline observation carried forward imputation based on drop-out reason

A series of sensitivity analyses were conducted to evaluate the robustness of the efficacy findings for the primary lung function endpoint. All of these sensitivity analyses confirmed the superiority of Bronchitol compared to control, with a consistent treatment effect ranging from 0.051 to 0.053 L over the 26-week treatment period in Study 303 (Figure 5).

Results of the tipping point analysis are described in Section 6.4.1.1.2.

Figure 5: Change from Baseline in FEV_1 (L): Forest Plot of Main and Sensitivity Analyses over the 26-Week Treatment Period (≥18 Years, ITT Set)



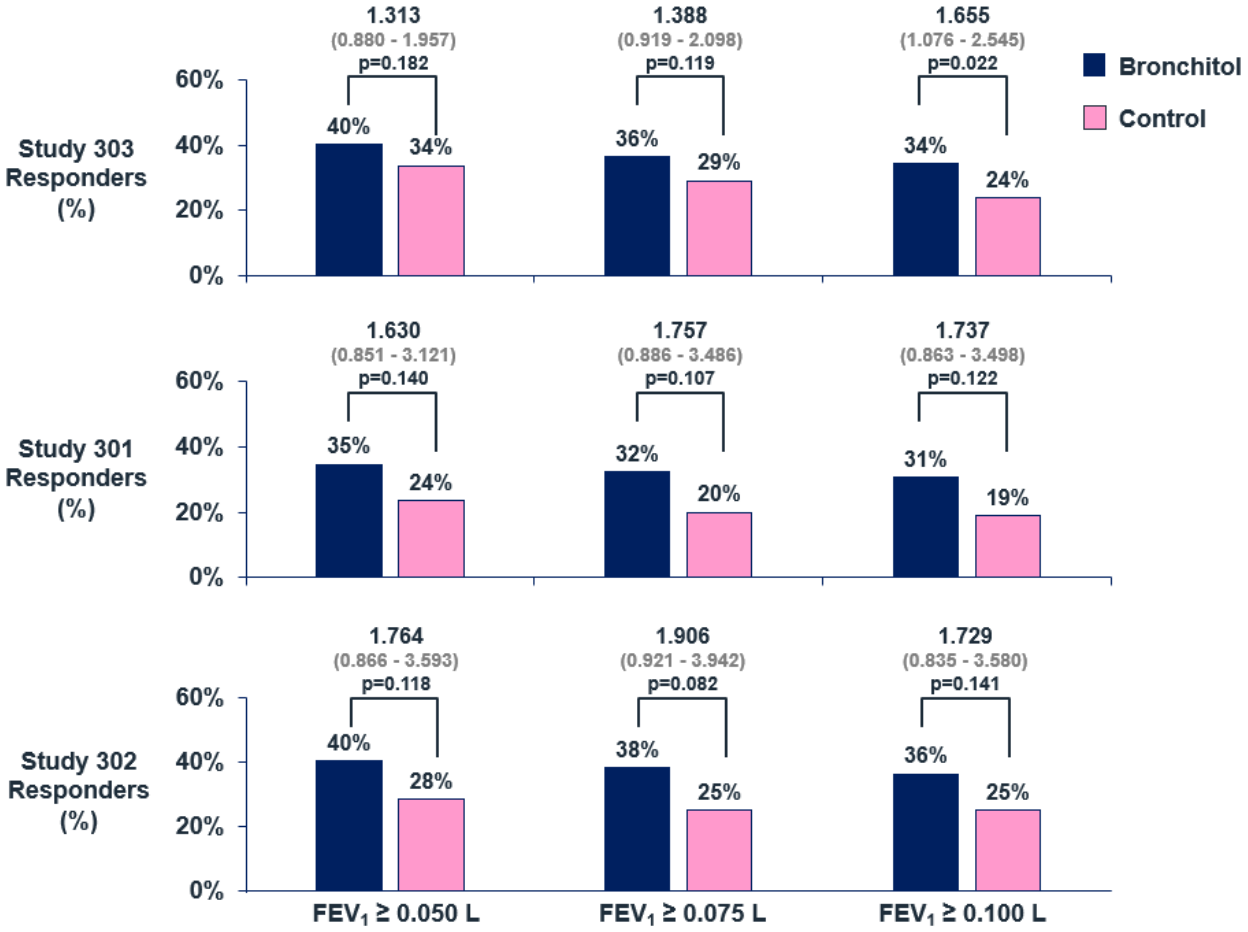
BOCF=Baseline observation carried forward; CI=Confidence interval; ITT=Intent-to-treat; MMRM=Mixed model repeated measures; PMM=Pattern mixture model

1.4.2.2 FEV_1 Responder Analyses

An additional pre-specified sensitivity analysis considered the percentage of patients responding to treatment at Week 26. At the thresholds of an improvement of 0.050 L, 0.075 L, and 0.100 L in Study 303, the percentage of patients who were FEV_1 responders at Week 26 was higher in the Bronchitol group compared to control (Figure 6). At the threshold of 0.100 L, 34.4% of patients treated with Bronchitol were responders compared with 23.8% of patients in the control group.

When identical statistical methods were applied to Studies 301 and 302, similar responder benefits were observed (Figure 6).

Figure 6: FEV_1 Responders at Week 26 in the Phase 3 Studies (≥18 years, ITT Set)



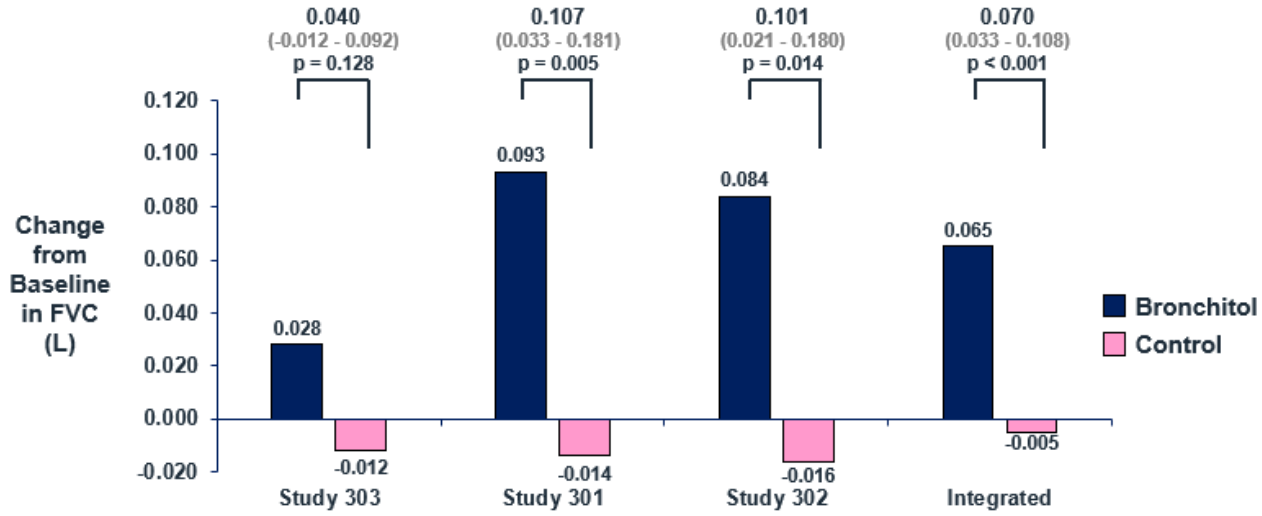
1.4.2.3 *Secondary Endpoints*

Pulmonary Function Secondary Endpoints

Secondary endpoints assessing pulmonary function supported the benefit of Bronchitol. In Study 303, the difference between treatments in FVC was numerically in favor of the Bronchitol group compared to control with an adjusted mean difference of 0.040 L (95% CI: -0.012; 0.092), p=0.128.

A favorable mean difference was also observed in Study 301 and Study 302 (Figure 7).

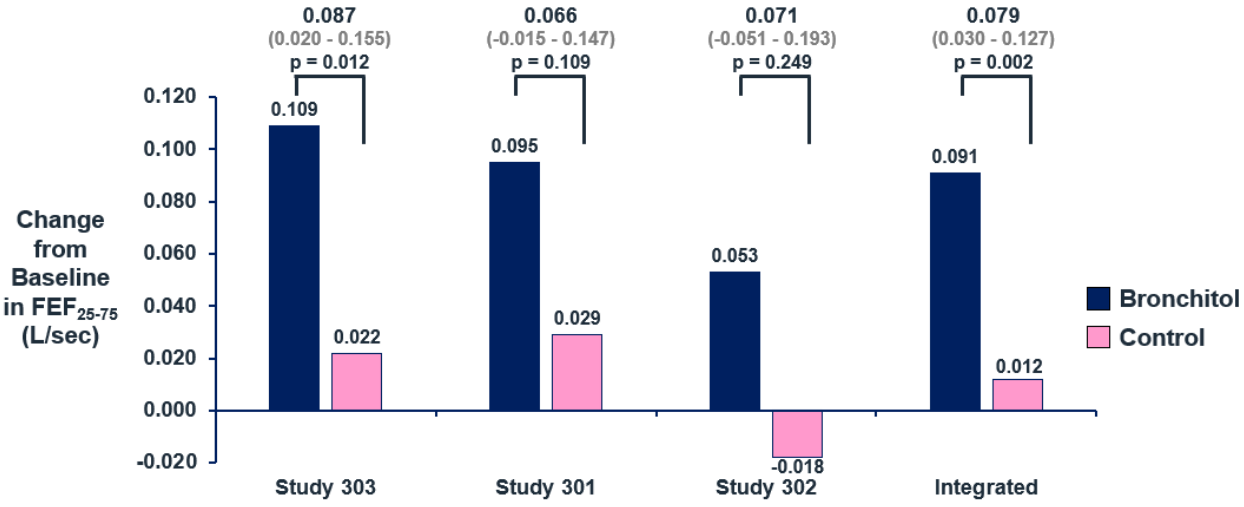
Figure 7: Change from Baseline in FVC over the 26-Week Treatment Period in Phase 3 Studies (≥18 years, ITT Set)



Mixed Model Repeated Measures with baseline observation carried forward imputation based on dropout reasons

Observed improvements in FEF_{25-75} also support the benefits on pulmonary function with Bronchitol treatment (Figure 8). In Study 303, the difference between treatments was in favor of Bronchitol compared to control, with an adjusted mean difference (95% CI) of 0.087 L/s (0.020; 0.155). A positive treatment difference was also observed in adult patients in Studies 301 and 302.

Figure 8: Change from Baseline in FEF_{25-75} over the 26-Week Treatment Period in Phase 3 Studies (≥18 years, ITT Set)



Mixed Model Repeated Measures with baseline observation carried forward imputation based on dropout reasons

Other Secondary Endpoints

In Study 303, the majority of patients did not experience a PDPE, which was defined as patients being treated with intravenous (IV) antibiotics because of four or more pre-specified signs or symptoms (described in Section 6.1.4.2); only 13.4% and 13.6% of patients in the Bronchitol and control arms, respectively, experienced one or more PDPE. No difference between the treatment groups was observed in PDPE rates over the 26-week treatment in Study 303 (adjusted rate ratio of Bronchitol compared to control [95% CI] of 1.194 [0.714; 1.997]); the rate of PDPE was similar between treatment groups in Studies 301 or 302.

Symptoms of CF were assessed using the CFQ-R, focusing on the respiratory domain. In all three Phase 3 studies, there was no appreciable change from baseline in score in either treatment group, as represented by Study 303: Bronchitol group 0.02 (95% CI: -1.91; 1.95), control group -0.56 (95% CI:-2.40; 1.27).

1.5 Safety Findings

The safety presentation in this briefing document includes pooled safety data from patients who received at least one dose of study drug in the three Phase 3 studies (Studies 301, 302, and 303), forming the Safety Set, which considers the adult population only (ie, patients aged ≥18 years), in alignment with the proposed indication for Bronchitol.

In the Safety Set, 896 adult patients were evaluated by the MTT. Of the 824 patients who successfully completed the MTT, 761 were randomized and received either Bronchitol 400 mg BID (414 patients) or control (347 patients) (Table 3). At the end of the 26-week double-blind treatment, an additional 94 patients from the control groups of Studies 301 and 302 were allocated to receive Bronchitol 400 mg BID during the open-label extension phases. A total of 508 patients were exposed to Bronchitol 400 mg BID, and 313 (61.6%) were treated for ≥6 months.

Table 3: Bronchitol Exposures in Adult Patients in the Phase 3 Studies (≥18 Years)

Total from Phase 3 Studies	**Patients (N)**
Received mannitol tolerance test	896
Passed mannitol tolerance test	824
Randomized and treated with Bronchitol	414
Continued on Bronchitol in open-label extension	130
Control patients treated with Bronchitol in open-label extension	94
Patients treated with Bronchitol 400 mg BID exposure (Double-blind period or open-label extension)	508
> 6 months	313

BID= Twice daily

1.5.1 Review of Adverse Events

The safety profile of Bronchitol in adult patients with CF has been well-characterized in three Phase 3 studies, and the AEs observed were mostly mild to moderate, manageable, and included events that would be anticipated to occur in this patient population. A summary of AEs in the Safety Set is shown in Table 4, and demonstrates that the overall safety profile was similar in the Bronchitol and control groups. Patients reported similar rates of AEs, severe AEs, and serious AEs (SAEs), while more patients receiving Bronchitol discontinued study drug than control. One death occurred in the Safety Set in a patient randomized to the control group in Study 303 and was due to a pulmonary exacerbation. Additional details on this event are in Section 7.8.

Table 4: Summary of Adverse Events in Phase 3 Studies (≥18 Years, Safety Set)

Category, n (%)	**Pooled Safety (Adult ≥ 18 Years)**	
	Bronchitol N=414	**Control N=347**
Patients with ≥1 AE	321 (77.5)	256 (73.8)
Patients with ≥1 severe AE	55 (13.3)	44 (12.7)
Patients with ≥1 serious AE	78 (18.8)	64 (18.4)
Patients with ≥1 AE leading to permanent discontinuation of study medication [a]	51 (12.3)	30 (8.6)
Patients with AE leading to death	0 (0.0)	1 (0.3)

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.
AE=Adverse event

In the Safety Set, the proportion of patients with ≥1 AE was similar in the Bronchitol (77.5%) and control (73.8%) groups (Table 5). The most commonly reported AE was condition aggravated (the Preferred Term [PT] for pulmonary exacerbation), which was reported in 31.9% of patients in the Bronchitol group and 32.9% of patients in the control group. Other frequently reported AEs included cough, headache, and hemoptysis. Cough was reported in a slightly higher percentage of patients in the Bronchitol group (15.0%) than in the control group (10.7%), as might be expected from the mechanism of action of the drug. Headache and hemoptysis were reported in similar percentages in both treatment groups.

Table 5: Adverse Events in ≥5% of Patients in Either Treatment Group (≥18 Years, Safety Set)

Preferred Term, n (%)	Pooled Safety (Adult ≥18 Years)	
	Bronchitol N=414	Control N=347
Patients with ≥1 AE	321 (77.5)	256 (73.8)
Condition aggravated	132 (31.9)	114 (32.9)
Cough	62 (15.0)	37 (10.7)
Headache	44 (10.6)	48 (13.8)
Hemoptysis	43 (10.4)	33 (9.5)
Nasopharyngitis	30 (7.2)	25 (7.2)
Oropharyngeal pain	29 (7.0)	15 (4.3)
Bacteria sputum identified	28 (6.8)	16 (4.6)
Upper respiratory tract infection	23 (5.6)	21 (6.1)
Lower respiratory tract infection	18 (4.3)	18 (5.2)

AE=Adverse event

The incidence of SAEs was also similar in patients in the Bronchitol and control groups (18.8% and 18.4%, respectively) (Table 6). The most common SAE was condition aggravated (PT for pulmonary exacerbation), which was reported in 13.3% of patients in the Bronchitol group and 11.2% of patients in the control groups. The second most common SAE was hemoptysis, which was reported by similar numbers of patients in both treatment groups. All other SAEs were reported in few patients and in similar proportions in both treatment groups.

Table 6: Serious Adverse Events in ≥1% in Either Treatment Group (≥18 Years Safety Set)

Preferred Term, n (%)	Pooled Safety (Adult ≥18 Years)	
	Bronchitol N=414	Control N=347
Patients with ≥1 serious AE	78 (18.8)	64 (18.4)
Condition aggravated	55 (13.3)	39 (11.2)
Hemoptysis	6 (1.4)	4 (1.2)
Lower respiratory tract infection	5 (1.2)	3 (0.9)
Pneumonia	1 (0.2)	4 (1.2)

Note: Bronchospasm not shown because reported in <1% of patients (1 [0.2%] Bronchitol, 0 Control).
AE= Adverse event

The proportion of patients who permanently discontinued study medication due to an AE was higher in the Bronchitol group (12.3%) compared with control (8.6%) (Table 7). Cough, including productive cough, was the most frequently reported AE leading to permanent discontinuation of study medication and was reported in a higher percentage of patients in the Bronchitol group (5.3%) than in the control group (2.6%).

Table 7: Adverse Events Leading to Permanent Discontinuation of Study Medication in > 1 Patient in Either Treatment Group (≥18 Years, Safety Set)

Preferred Term, n (%)	Pooled Safety (Adult ≥18 Years)	
	Bronchitol N=414	Control N=347
Patients with ≥1 AE leading permanent discontinuation of study medication [a]	51 (12.3)	30 (8.6)
Cough [b]	22 (5.3)	9 (2.6)
Condition aggravated	13 (3.1)	9 (2.6)
Hemoptysis	7 (1.7)	4 (1.2)
Chest discomfort	4 (1.0)	3 (0.9)
Bronchospasm	2 (0.5)	0 (0.0)
Fatigue	2 (0.5)	0 (0.0)
Oropharyngeal pain	2 (0.5)	0 (0.0)
Headache	1 (0.2)	2 (0.6)
Wheezing	1 (0.2)	3 (0.9)

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.
b Includes PTs of "cough" and "productive cough"
AE= Adverse event

1.5.2 Adverse Events of Special Interest

Cough, pharyngolaryngeal pain, hemoptysis, bronchospasm, and pulmonary exacerbations are common events in patients with CF or may be expected based on the known effects of Bronchitol. Therefore, these events were designated as AEs of special interest (AESIs). The AESIs were coded under the following PTs:

- Cough: "cough" and "productive cough"
- Pharyngolaryngeal pain: "oropharyngeal pain"
- Hemoptysis: "hemoptysis"
- Bronchospasm: "bronchospasm" and "bronchial hyperreactivity"
- Pulmonary Exacerbation: "condition aggravated"

It should be noted that the reporting of pulmonary exacerbations was based on investigator assessment, which differs from the PDPE definition used as a secondary efficacy assessment.

As shown in Table 8, AESIs of cough and pharyngolaryngeal pain occurred more often with Bronchitol than control, while hemoptysis, bronchospasm, and pulmonary exacerbations were reported in similar proportions of patients in each treatment group. Section 7.9 provides additional details for each AESI.

Table 8: Summary of Adverse Events of Special Interest (≥ 18 Years, Safety Set)

Patients with ≥1 AESI	Pooled Safety Set	
	Bronchitol N=414	**Control N=347**
Cough [a]	69 (16.7)	43 (12.4)
Pharyngolaryngeal Pain	29 (7.0)	15 (4.3)
Hemoptysis	43 (10.4)	33 (9.5)
Bronchospasm [b]	4 (1.0)	2 (0.6)
Pulmonary Exacerbation	132 (31.9)	114 (32.9)

a Coded under PT of "cough" and "productive cough"
b Coded under PT of "bronchospasm" and "bronchial hyperreactivity"
AESI=Adverse event of special interest; PT=Preferred Term

A summary of the conclusions based on the AESI analysis is as follows:

- Cough is common in patients with CF and is also an expected event based on the known effects of Bronchitol. Consistent with the mechanism of action of Bronchitol, cough may facilitate airway mucus clearance.
- Pharyngolaryngeal pain was an expected event, as it is associated with the use of inhaled powders in the management of CF.
- Hemoptysis is common among patients with CF due to airway infection and inflammation. The incidence of hemoptysis with Bronchitol treatment was similar to control and did not exceed the expected background rates for adults based on the published literature (Fuchs 1994, Ramsey 1999, Konstan 2011, Thompson 2015).
- Bronchospasm may occur following the inhalation of any medicinal product, including nebulized solutions, aerosols, or dry powders. Few events of bronchospasm were reported, which may be attributed to use of the MTT prior to initiation of Bronchitol treatment as well as the pre-dose inhalation of a short-acting beta-agonist bronchodilator.
- Pulmonary exacerbations may occur in patients with CF due to chronic infection and inflammation characteristics of CF lung disease. Pulmonary exacerbations were therefore expected, and the proportions of patients affected were similar between treatment groups.

1.5.3 Open-Label Safety Experience

Open-label safety data were derived from a total of 224 patients who received Bronchitol 400 mg BID during up to 52 weeks of open-label experience in Study 301 and up to 26 weeks in Study 302. The median duration of exposure to Bronchitol in the open-label extensions was 6.0 months. During open-label treatment with Bronchitol, 87.1% of patients experienced ≥1 AE.

The frequency of AESIs of cough, pharyngolaryngeal pain, hemoptysis, and bronchospasm during open-label treatment with Bronchitol was similar to that observed during the randomized

periods of the studies, while AEs of pulmonary exacerbation were reported in a higher proportion of patients (Table 9).

Table 9: Adverse Events of Special Interest in Double-Blind Treatment and Open-Label Extensions (≥18 years)

	Phase 3 Safety Set		Open-Label Extensions
Patients with ≥1 AE	**Bronchitol N=414**	**Control N=347**	**Bronchitol N=224**
Cough [a]	69 (16.7)	43 (12.4)	29 (12.9)
Pharyngolaryngeal Pain	29 (7.0)	15 (4.3)	10 (4.5)
Hemoptysis	43 (10.4)	33 (9.5)	23 (10.3)
Bronchospasm [b]	4 (1.0)	2 (0.6)	3 (1.3)
Pulmonary Exacerbation	132 (31.9)	114 (32.9)	99 (44.2)

a Coded under PT of "cough" and "productive cough"
b Coded under PT of "bronchospasm" and "bronchial hyperreactivity"
PT=Preferred Term

1.5.4 Post-Marketing Experience

Global post-approval cumulative exposure of Bronchitol through 31 December 2018 is estimated to involve approximately 8,000 patients.

No safety signal has been identified in the post-marketing setting.

1.6 Benefit-Risk Summary

Despite advancements in therapeutic approaches such as CFTR modulators, patients with CF still require additional treatments for the downstream manifestations of the disease, such as mucoactive therapies that mechanistically target airway clearance. A medical need exists for an easy-to-use treatment that intervenes early in the pathophysiology of CF to improve lung function.

In adult patients with CF, Bronchitol provides a unique mechanism to improve mucus clearance and pulmonary function, a prognostic indicator for morbidity and mortality.

Bronchitol demonstrated consistent and clear improvements in lung function in adults in three comparable Phase 3 studies. Over the 26-week double-blind treatment period, the analyses of the changes from baseline in FEV_1, demonstrated superiority of Bronchitol versus control in adults in each individual study and in the integrated analysis. The improvements were supported by sensitivity analyses and secondary pulmonary function endpoints.

The safety profile of Bronchitol in adult patients has been well-characterized in the three Phase 3 studies. Most AEs were mild-to-moderate in severity, manageable, and included events that would be anticipated to occur in this patient population. In addition, the safety profile of Bronchitol is supported by 8 years of post-approval experience.

Overall, data from the large clinical development program support the positive benefit-risk profile of Bronchitol for the management of CF to improve pulmonary function in adult patients with CF.

2 DISEASE BACKGROUND AND CURRENT TREATMENT OPTIONS

Summary

- Cystic fibrosis is non-curable, life-shortening, genetic disease caused by mutations in the CFTR gene, primarily affecting the lungs.
- Cystic fibrosis affects approximately 30,000 patients in the US, with more than 800 new cases diagnosed each year. The predicted median survival is approximately 44 years, and the number of adult patients continues to increase.
- In the lungs, dysfunctional CFTR genes lead to dehydration of the airway surface liquid layer and reduction in mucociliary clearance. This leads to accumulation of thick, adhesive mucus which causes chronic bronchopulmonary infection and impaired lung function.
- A primary aim in the treatment of CF lung disease is to improve lung function, which is commonly measured by FEV_1. Pulmonary function predicts morbidity and mortality in patients with CF.
- Chronic management of CF focuses primarily on mitigation of the downstream manifestations of reduced CFTR activity and involves multiple therapies, leading to a high treatment burden.
- Adult patients with CF need a portable, easy-to-use treatment that can improve mucus clearance and pulmonary function.

2.1 Overview of Cystic Fibrosis

2.1.1 Etiology and Prognosis

Cystic fibrosis is an autosomal recessive, non-curable, life-shortening condition caused by mutations in the CFTR gene, which encodes a chloride ion channel expressed in many different organs, primarily the lung. In the US, CF affects approximately 30,000 patients with more than 800 new cases diagnosed each year (CFF Registry 2017). Over 90% of patients with CF are Caucasian, and most US patients are now diagnosed by newborn screening.

The predicted median survival for patients with CF in the US is approximately 44 years, and the number of adults with CF continues to increase. In 2017, adults accounted for 53.5% of the CF population, compared with 29.8% in 1987 (CFF Registry 2017).

The basic defect of CF is associated with a failure to transport chloride through the CFTR ion channel and a tendency to hyper-absorb sodium through epithelial sodium channels. In the lungs, a dysfunctional CFTR leads to dehydration of the airway surface liquid layer, formation of adhesive and tenacious mucus, and reduction in mucociliary clearance (Elborn 2016, Kolodziej 2017, Kreda 2012). Ineffective mucus clearance causes recurrent and chronic bacterial infections, inducing persistent inflammation, and airway wall damage leading to impaired lung function (Boucher 2007).

Chronic progressive lung disease is indeed the main negative prognostic factor in patients with CF (Salvatore 2011). Patients with CF have progressive cycles of infection and inflammation, which lead to irreversible damage to the architecture of the lung, significant deterioration in pulmonary function, and ultimately respiratory failure (Strausbaugh 2007). In patients with CF, pulmonary function progressively declines over their lifetime, at an average rate of 1-2% per year, although for some patients this deterioration may be considerably faster (Liou 2010). Respiratory failure accounts for more than 80% of mortality in patients with CF (Flume 2012).

Consequently, a primary therapeutic goal in the treatment and management of CF includes increased airway hydration combined with a better clearance of mucus in order to improve lung function (Boucher 2007, Daviskas 2010a)

2.2 Cystic Fibrosis Lung Function Endpoints

Within the context of CF pulmonary disease, lung function is the most prominent measure of disease severity, progression, and therapeutic efficacy (Szczesniak 2017). The primary and most well-established spirometric parameter of interest in CF is FEV_1. The strong relationship between FEV_1 and the pathophysiology of CF pulmonary disease, combined with its ability to be objectively and reliably measured relative to other endpoints, has made FEV_1 a key endpoint for determination of efficacy of treatment modalities in CF clinical studies (Liou 2010, Mayer-Hamblett 2007, VanDevanter 2012). Notably, all recently approved CF products intended to improve lung function were approved based on clinical studies that utilized FEV_1 as a primary endpoint.

Moreover, FEV_1 is the strongest clinical predictor of survival among patients with CF (Szczesniak 2017). Decreased FEV_1 is associated with increased morbidity and mortality (Corey 1996, Liou 2001, Zemanick 2010).

Additional spirometer parameters include FVC and FEF_{25-75}. FVC, a measure of total lung capacity, may be relevant in patients with more severe lung disease, while the FEF_{25-75} has been reported to be more sensitive than FEV_1 at detecting obstruction of the small airways, which have been suggested to play a key role in the early pathophysiological changes of CF lung disease (Bakker 2013, Wagener 2015).

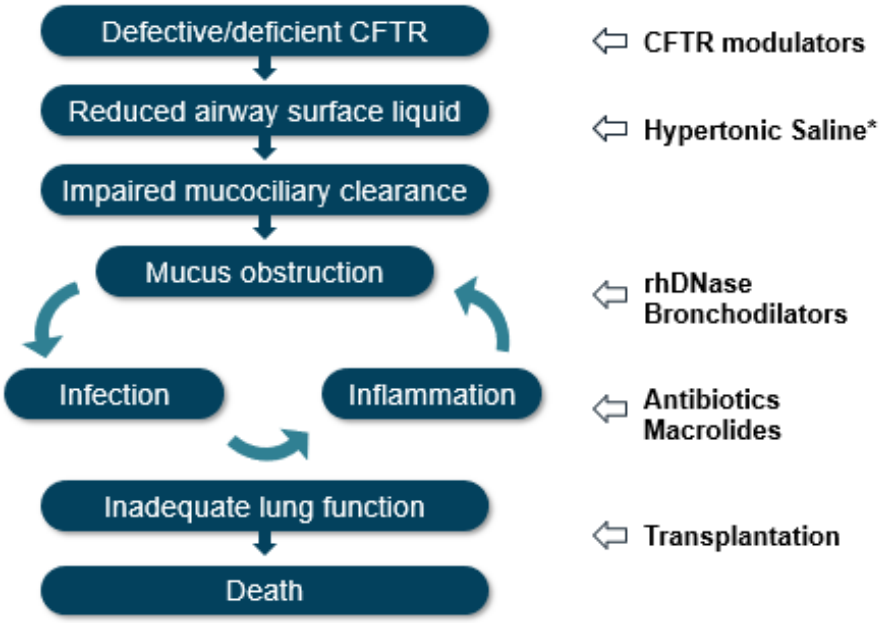
2.3 Current Treatment Options

The last two decades have seen the addition of effective medications and therapies for the management of CF lung disease. Although these therapies have improved the overall health of patients with CF and they are clearly part of the reason that expected survival has increased, there remains no curative therapy for CF.

2.3.1 Spectrum of Available Cystic Fibrosis Therapies

Several approaches that target different steps of the pathophysiological pathway of lung disease in CF include targeting the genetic defect, improving mucociliary clearance, suppressing the growth of bacterial pathogens, and attenuating airway inflammation (Figure 9) (Zemanick 2010).

Figure 9: Cystic Fibrosis Pathophysiological Pathway and Recommended Therapies



*Hypertonic saline is not approved in the US for treatment of cystic fibrosis.
CFTR=Cystic Fibrosis Transmembrane Conductance Regulator; rhDNase=Recombinant human deoxyribonuclease

Mechanical clearance of secretions from the airways is a primary approach for patients with CF, with a number of airway clearance therapies (ACTs) recommended in the current guidelines including positive expiratory pressure, high frequency chest wall oscillation, and exercise (Flume 2009).

Established CF treatments target downstream manifestations of the primary genetic defect (Hudock 2017). As an adjunct to ACTs, inhaled aerosol therapy, including antibiotics, mucoactive agents, and bronchodilators along with oral anti-inflammatory drugs are recommended. However, there are a limited number of approved mucoactive agents, which are intended to modify mucus production, secretion, composition, or its interactions with the mucociliary epithelium.

CFTR modulators are novel therapies available for use in patients with specific genetic mutations; they improve the function of CFTR and have been approved to mitigate the effect of specific CF-causing mutations. However, CFTR modulators have not obviated the need for other therapies and consequently the long-term management of CF is still focused on the mitigation of downstream manifestations.

2.3.2 Overview of Mucoactive Inhaled Therapies

Prescribed therapies for patients with CF mainly include the mucolytic rhDNase (dornase alfa; Pulmozyme®) and hypertonic saline, both of which are administered by inhalation via a nebulizer. Mechanistically, rhDNase alters the sputum viscosity by digesting high molecular weight DNA that is typically released in the CF airways by dead neutrophils. However, rhDNase was not shown to significantly improve mucociliary clearance (Robinson 2000).

Although recommended in CF guidelines, nebulized hypertonic saline is not an FDA-approved treatment. In clinical practice it is used in a non-standardized range of concentrations (3-7%) and can be difficult for patients to tolerate at high concentrations (Robinson 1997). Hypertonic saline acts via an osmotic mechanism of action to increase airway surface liquid and improve mucociliary clearance (Donaldson 2006; Figure 9). Inhaled hypertonic saline has also been demonstrated to improve lung function in patients with CF in a systematic review (Wark 2009). The recognized side effect profile of hypertonic saline in patients with CF is characterized by more frequent coughing, sore throat, chest tightness, and bronchospasm leading to tolerability issues and poor adherence (Ratjen 2006, Suri 2001, Wark 2009).

Both rhDNase and hypertonic saline require time to prepare and administer. Patients are reported to spend up to 40 minutes per day using nebulizers in a BID regimen (Sawicki 2009). Additional time is required for cleaning of the nebulizer to lower the potential risk of infection or reinfection of patients caused by microbial contamination (Blau 2007). As a result of the burden of daily therapy experienced by patients with CF, treatment adherence to such nebulized therapies may be poor.

2.3.3 Treatment Regimens in Cystic Fibrosis

Due to the progressive nature of CF, patients are typically treated with multiple therapies in an effort to maintain lung function. Individualized treatment is based on response, tolerability, and acceptability by patients. The use of multiple therapies results in a high treatment burden for patients and is also reflected by recent drug approvals in CF which have all been examined against a background of standard therapy.

According to a survey of adult patients with CF, patients reported taking a median of seven medications and spending almost two hours each day on CF therapies (Sawicki 2009). Nebulized treatments, in particular, may contribute to the burden of therapy due to the time required for set up, administration, and cleaning of equipment, as noted above.

2.4 Unmet Medical Need

Currently, there is no curative treatment for CF. While CFTR modulators are available for patients with specific gene mutations, there remains a need for additional therapies to address one or more of the various disease-related issues, including infection, inflammation, disease progression, and extrapulmonary complications of CF.

Despite currently available therapies, some patients with CF may still be unable to adequately clear mucus secretions (West 2018). Therefore, adult patients with CF need a portable and easy-to-use treatment that can improve mucus clearance and pulmonary function. A new mucoactive agent would allow patients with CF to tailor their treatment regimen and provide the best opportunity for overall treatment success while optimizing outcomes in this life-shortening disease.

3 PRODUCT DESCRIPTION

Summary

- The proposed indication for Bronchitol is for the management of CF to improve pulmonary function in patients 18 years and older in conjunction with standard therapies; the recommended dosing is 400 mg BID.
- Bronchitol consists of two components: the drug product, a spray dried mannitol powder in hard capsules, and a DPI.
- Mannitol is a naturally occurring molecule that is classified by the US FDA as a GRAS excipient for food substances.
- The osmotic properties of mannitol increase the hydration of airway surface liquid, which results in increased mucociliary clearance in patients with CF, and in turn to improved lung function.

3.1 Proposed Indication and Dosing

As proposed, Bronchitol is indicated for the management of CF to improve pulmonary function in patients 18 years and older in conjunction with standard therapies.

The proposed dose of Bronchitol is 400 mg of dry powder mannitol, which is to be administered by oral inhalation of the contents of ten 40 mg hard gelatin capsules BID using a DPI.

3.2 Administration

Each Bronchitol capsule contains 40 mg of spray dried D-mannitol powder with no excipients. The patient sequentially inhales ten 40 mg capsules. The inhalation process for the full dose takes approximately 5 minutes to complete.

3.3 Product Overview

3.3.1 Biopharmaceutics

Mannitol is a naturally occurring polyol (sugar alcohol) found in most vegetables and used extensively as a food additive. Mannitol is also commonly used as a pharmaceutical excipient in many oral products, as well as in some inhaled products (Rowe 2009). Mannitol is classified by the US FDA as a GRAS excipient for food substances, and the World Health Organization (WHO) concluded that mannitol was safe at a dietary intake up to 50 mg/kg (3 to 4 g/day) (International Program on Chemical Safety 2018).

The osmotic properties of mannitol increase the hydration of airway surface liquid, which results in increased mucociliary clearance in patients with CF (Nolan 2016).

Mannitol is a stable substance that has good flow characteristics as a powder and resists moisture absorption at relative high humidity, and therefore is a suitable substance to encapsulate for

inhalation. A unique spray-drying process produces primary particle size distributions in the desired range for delivery to the lung (mean aerodynamic particle diameter ~3 μm) (Li 2014).

3.3.2 Dry Powder Inhaler Device

The inhaler device is the breath actuated, Dry Powder RS01 Inhaler Model 7 (Inhaler) manufactured by Plastiape S.p.A. The inhaler is a manually operated dry powder delivery system. Each inhaler is used for one week and discarded.

The adequacy of patient inspiratory efforts with the proposed inhaler was confirmed in an open observational non-drug study (Study DPM-OSM-403) in children and adults with CF.

3.3.3 Marketing Approvals for Bronchitol

Bronchitol was first approved in 2011 in Australia. As of December 2018, it has been approved in 35 countries for the treatment of adult patients with CF, including in the European Economic Area (EEA), Israel, and Serbia. In addition, Bronchitol is approved for use in both adult and pediatric patients with CF in Australia and Russia.

Another inhaled mannitol preparation, Aridol®, is marketed by Pharmaxis in the US. Aridol is used to test for bronchial hyperresponsiveness to assist in the diagnosis of asthma. With the exception of dose, the preparation of mannitol in Aridol is exactly the same as in Bronchitol. With Aridol, the maximum total dose of inhaled mannitol is higher (635 mg) and is administered in a stepwise fashion on a single occasion in an acute testing scenario.

3.4 Mechanism of Action

Nonclinical in vivo data demonstrated a significant reduction in the surface tension and increased wettability of mucus after inhaled mannitol administration. These findings suggest that mannitol may act osmotically to cause water to flow from tissues into the airway lumen to reduce the thickness and adhesiveness of the airway mucus (Daviskas 2005).

Additionally, Bronchitol may increase mucus flowability by disrupting hydrogen bonds that join the oligosaccharides in the mucin macromolecules, thereby affecting the viscosity of the mucus by reducing the number of entanglements formed by mucin polymers (Daviskas 2005, King 1997, Feng 1998). An improvement in the rheology of mucus could favor ciliary transportability and cough clearance (King 1997, Feng 1998). Several studies have shown that inhaled mannitol increases mucociliary clearance, including studies in healthy subjects as well as patients with asthma, bronchiectasis, and CF (Daviskas 1997, Daviskas 2001, Robinson 1999). Productive cough induced by inhaled mannitol is also reported to positively contribute to airway clearance (Robinson 1999).

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- The original NDA for Bronchitol was submitted in May 2012 for management of CF to improve pulmonary function in adult and pediatric patients with CF.
- A CRL was issued by the FDA stating that the Phase 3 studies did not provide a favorable benefit-risk ratio and an additional study was needed.
- The NDA for Bronchitol in adult patients with CF was re-submitted in December 2018 after a third Phase 3 study (Study 303) was completed in response to the CRL.
    - Study 303 was conducted to demonstrate the efficacy and safety of Bronchitol following inconsistent efficacy results in Studies 301 and 302 which included both pediatric and adult patients.
- The clinical development program for Bronchitol included three randomized, controlled, parallel group Phase 3 studies in patients with CF (Studies 301, 302, and 303).
- The key Phase 2 dose-relationship study in patients with CF (Study 202) identified the Bronchitol dose for Phase 3.

4.1 Regulatory History

Development of Bronchitol has been conducted as a partnership between Pharmaxis, Ltd and Chiesi. Table 10 provides an overview of key FDA interactions and discussion topics.

Table 10: Overview of Key FDA Interactions During Bronchitol Clinical Development

Date	Event
13 July 2005	Orphan Designation granted
17 May 2012	Original NDA Submission by Pharmaxis, Ltd • Cross-reference to Aridol® NDA 22368 • Proposed indication: "[inhaled mannitol] for the use in the management of CF to improve pulmonary function" in adult and pediatric patients with CF. • Supported by two Phase 3 studies (301 and 302) in children and adults with CF
30 January 2013	Pulmonary-Allergy Drugs Advisory Committee Meeting • Discussed benefit/risk, specifically in pediatric population, and missing data
18 March 2013	Complete Response Letter • FDA request conduct of at least one adequate clinical study to show substantial evidence of efficacy in adult patients with CF and further evidence supporting the risk/benefit
17 May 2013	End of Review Meeting • Discussed need to conduct "tie breaker" study and study design including duration and endpoint to establish efficacy in adult patients • Based on feedback, Study 303 was conducted to address FDA concerns
26 November 2016	Pre-submission (Type B) meeting • Discussed integrated efficacy and safety analyses, statistical methods, handling of missing data, endpoints selection, and subgroup analyses
31 May 2017	Study 303 Statistical Analysis Plan Comments • Recommendations from FDA on supportive and sensitivity analyses: pattern mixture model imputation and tipping point analyses.
19 December 2018	NDA re-submission by Chiesi USA, Inc • Proposed indication: "[Bronchitol] for the use in the management of CF to improve pulmonary function" in adult patients with CF • Supported by three Phase 3 studies (301, 302, and 303) including adults with CF

CF=Cystic fibrosis; FDA=Food and Drug Administration; NDA=New Drug Application

Prior to the original NDA submission, the FDA and the Sponsor discussed the use of change in FEV_1 over 26 weeks as the primary efficacy endpoint in line with other CF studies and the use of inhaled mannitol 50 mg BID for the control in the Phase 3 Studies.

In May 2012, an NDA was submitted for Bronchitol for use in the management of CF to improve pulmonary function in adult and pediatric patients with CF. The NDA included the results from the first two Phase 3 studies (301 and 302), which were completed in 2010. Study 301 met the primary endpoint with a treatment difference of 0.083 L (95% CI: 0.039; 0.127), $p<0.001$ in favor of Bronchitol compared to control. The treatment difference for the primary endpoint in Study 302 was numerically in favor of Bronchitol compared to control with an increase of 0.054 L in (-0.002; 0.110), $p=0.059$.

Following submission of the NDA, a PADAC meeting was held on 30 January 2013. Discussion at the meeting focused on the high drop-out rate particularly in Study 301, missing data, rate of hemoptysis (especially in the pediatric population), and benefit-risk ratio in the pediatric population.

The FDA issued a CRL on 18 March 2013 stating that Studies 301 and 302 did not provide a favorable benefit-risk balance to support the use of Bronchitol in patients with CF 6 years of age and older. The determination of efficacy based on the two studies was not adequate because of

the frequent treatment-related early dropouts in Study 301, which were not accounted for in the primary statistical analyses, and the lack of statistical significance for the primary endpoint in Study 302. To address these concerns, FDA recommended conducting an additional adequate clinical study to show evidence of efficacy and safety in adult CF patients and to confirm an acceptable safety profile by including pre-specified criteria that address the specific safety concern of hemoptysis.

In the subsequent End of Review meeting, the FDA indicated that the clearest and most expedient regulatory path forward for the Bronchitol program would be to conduct a third "tie breaker" study to establish the efficacy of Bronchitol in patients with CF. The design of the study was recommended to be very similar to the previous two studies in terms of design, duration, and comparator, with proactive steps to minimize dropouts. The FDA strongly recommended that the study be performed in adults only (18 years of age and older).

Based on these discussions with FDA, Study 303 was conducted in adult patients with CF to support the findings from the earlier Phase 3 Studies 301 and 302; this new Phase 3 study was completed in 2017 and was discussed with the FDA as the primary basis of a planned NDA re-submission focused on the adult patient population. The analysis plan for the NDA re-submission was discussed with the FDA in 2016 at which time it was agreed the statistical methods of Study 303 should be applied to Studies 301 and 302 to determine an estimate of Bronchitol efficacy and safety compared to control in adult patients with CF.

In December 2018, as discussed with the FDA, the NDA was re-submitted with the proposed indication focused in the adult population including data from the recently-completed third Phase 3 study (Study 303) and an integrated analysis of all data in the adult population for all three Phase 3 studies.

4.2 Clinical Development Program

The clinical development program for Bronchitol included the following nine clinical studies:

- Three randomized, controlled, parallel-group Phase 3 studies in patients with CF
- Four randomized Phase 2 studies in pediatric and adult patients with CF
- Two Phase 1 pharmacokinetic (PK) studies in healthy subjects and patients with CF

The key Phase 3 and Phase 2 studies are described in Table 11.

Table 11: Bronchitol Phase 3 and Phase 2 Clinical Studies

Study Number	Patients Randomized	Design	Key Inclusion Criteria
Phase 3 Controlled Efficacy Studies			
301	N=324 n <18 yr=115 n ≥18 yr= 209	- Initial treatment phase: double-blind randomized, parallel group, controlled 26-week safety and efficacy phase Study Drug: Bronchitol, 400 mg BID Control: inhaled mannitol, 50 mg BID - Final treatment phase: open-label uncontrolled 26 to 52-week safety phase All patients received Bronchitol, 400 mg BID Primary Endpoint: Change in FEV_1 from baseline over 26 weeks	Patients >6 years of age with CF, and a baseline FEV_1 of between 30% and 90% of the predicted normal value
302	N=318 n <18 yr=161 n ≥18 yr=157	- Initial treatment phase: double-blind, randomized, parallel group, controlled 26-week safety and efficacy phase Study Drug: Bronchitol, 400 mg BID Control: inhaled mannitol, 50 mg BID - Final treatment phase: open-label uncontrolled 26-week safety phase All patients received Bronchitol, 400 mg BID Primary Endpoint: Change in FEV_1 from baseline over 26 weeks	Patients >6 years of age with CF, and a baseline FEV_1 of between 40% and 90% of the predicted normal value
303	N=423 n ≥18 yr=423	- Double-blind, randomized, parallel group, controlled 26-week safety and efficacy phase Study Drug: Bronchitol, 400 mg BID Control: inhaled mannitol, 50 mg BID Primary Endpoint: Change in FEV_1 from baseline over 26 weeks	Patients ≥18 years of age with CF, and a baseline FEV_1 of between 40% and 90% of the predicted normal value
Phase 2 Dose Relationship Studies			
201	N=39 n <18 yr=21 n ≥18 yr=18	A randomized, multicenter, double-blind, controlled, crossover, Phase 2 study Study Drug 420 mg inhaled mannitol BID for two weeks Control: Non-respirable mannitol BID for two weeks	Patients between 8 - 48 years of age with CF, and a baseline FEV_1 of between 40% and 80% of the predicted normal value or a decline in FEV_1 of >20% in the last 12 months
202	N=48 n <18 yr=29 n ≥18 yr =19	A randomized multicenter open-label, dose response crossover study, to determine the dose of inhaled mannitol required to generate clinical improvement in FEV_1 Study drug: 2 weeks each of 40 mg, 120 mg, 240 mg and 400 mg inhaled mannitol BID	Patients between 7-68 years of age with CF and a baseline FEV_1 between 40% and 90% of the predicted normal value or a decline in FEV_1 of >20% in the last 12 months.

5 CLINICAL PHARMACOLOGY

Summary

- The absolute bioavailability of mannitol powder following inhalation was approximately 59%.
- Following single oral and inhaled dosing of mannitol, maximum serum concentration was achieved within 2.5 hours.
- In studies with a similar formulation and device, lung deposition of inhaled mannitol is approximately 25%.
- Phase 3 dose selection of Bronchitol 400 mg BID was supported by Study 202. A 50 mg inhaled mannitol control was selected to allow for masking in the control group.

5.1 Pharmacokinetics

The PK characteristics of inhaled mannitol were determined from data provided by Studies 101 and 102, described in Table 12.

In healthy adult male subjects (Study 101), the absolute bioavailability of mannitol following inhalation was approximately 59%. Lung deposition studies with a similar formulation and device have demonstrated a 24.7% deposition of inhaled mannitol, confirming its delivery to the target organ (Glover 2006). There is no evidence that mannitol accumulates in the body.

Study 101 demonstrated that the systemic bioavailability from absorption of inhaled mannitol is similar to that of ingested mannitol.

Table 12: Design Features of Clinical Pharmacokinetic Studies

Study	Study Title	Study Population	Study Drug, Dose Route and Regimen	Primary Endpoints
101	A pharmacokinetic and bioavailability study of mannitol for inhalation using healthy subjects	18 healthy males Mean age (range): 27 years (19-48)	635 mg inhaled mannitol; 500 mg orally; 500 mg IV	PK parameters Relative and absolute bioavailability
102	Determination of the pharmacokinetics of inhaled mannitol after single and multiple doses in patients with CF	8 males, 10 females with CF Mean age (range): 16 years (6-32)	Inhaled mannitol: 400 mg Q.D. on Days 1 and 7; 400 mg BID on Days 2-6	Comparison of PK parameters after single and multiple dosing

BID=Twice daily; CF=Cystic fibrosis; IV=Intravenous; PK=Pharmacokinetic(s); Q.D.=Once daily

Following single oral and inhaled dosing in healthy subjects and patients with CF, mannitol was quickly absorbed, and the rate and extent of absorption were similar. Serum mannitol levels (mean time to peak plasma concentration [T_{max}] values) peaked at 2.42 hours in adult subjects post-dosing. Between subject variability in mean maximum observed plasma concentration (C_{max})

values in adult subjects ranged from 15 to 29%. Between subject variability in mean area under the plasma concentration versus time curve ($AUC_{0-\infty}$) values (Day 1) in adult subjects was 22%.

The PK parameter estimates in patients with CF (Study 102) were similar to the pharmacokinetics of mannitol observed in healthy subjects.

In non-clinical toxicology studies, there was no evidence of mannitol accumulation. Since the low level of accumulation noted in Study 102 was not significant, and there is no other evidence of accumulation in the body, distribution of inhaled mannitol was not examined in human PK studies.

5.2 Pharmacodynamics

Inhaled mannitol has been shown to increase the clearance of airway mucus in CF patients (Robinson 1999). Once inhaled mannitol is delivered into the lungs, the resultant osmotic gradient draws water from the surrounding tissues into the airway lumen. This has the following benefits (Robinson 1999, Daviskas 1997, Daviskas 1999, Daviskas 2010a):

- Rehydrates depleted underlying airway surface liquid layer;
- Breaks down bonds within mucus to make it less viscous;
- Modifies surface properties of mucus to improve transport;
- Increases cilia beat frequency;
- Promotes productive cough and improves cough effectiveness.

The net effect is the improvement of airway mucus clearance, and therefore improved lung function (Daviskas 1997, Daviskas 2010b).

5.3 Use with Other Inhaled Therapies

Bronchitol has been studied in clinical studies in combination with other inhaled general respiratory and CF medications. In the Phase 3 studies with Bronchitol, patients were allowed to continue prescribed CF therapies (eg, inhaled antibiotics such as tobramycin, inhaled mucolytic rhDNase, bronchodilators, and inhaled corticosteroids). From the Phase 3 clinical studies, there was no indication that the safety of inhaled mannitol was altered by these other medications commonly used in CF and the efficacy demonstrated was therefore on top of conventional therapy for the disease.

5.4 Drug-Drug Interactions

No formal drug interaction studies have been conducted. Bronchitol has been safely used in clinical studies in conjunction with standard CF therapies directed to the lung such as antibiotics, mucolytics, bronchodilators, and inhaled corticosteroids, and also other systemic therapeutics including pancreatic enzymes, vitamins, systemic corticosteroids and analgesics.

More specifically, the concomitant use of the commonly used mucolytic, rhDNase, with Bronchitol did not adversely affect the safety profile of Bronchitol as assessed by the frequency of all AEs, severe AEs, and SAEs in the Phase 3 studies.

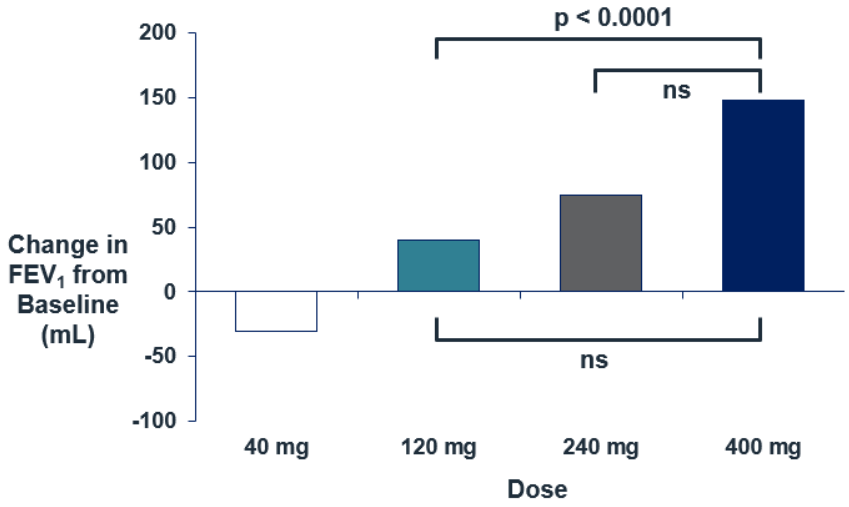
5.5 Dose Selection for Phase 3 Studies

5.5.1 Phase 2 Dose-Finding Assessment

Study 202 investigated the dose response of Bronchitol on lung function in patients with CF. It was an open-label, randomized, multicenter crossover study of Bronchitol at doses of 40, 120, 240, and 400 mg. FEV_1 was measured at baseline and after 2 weeks of administration. Each treatment period was followed by a 1-week washout period.

After two weeks of administration, there was a dose-dependent increase in FEV_1 and FVC (Figure 10). A statistically significant difference between the 400 mg and 40 mg doses was observed in the relative change from baseline in FEV_1 and FVC. The differences between the Bronchitol 400 mg dose and the Bronchitol 120 mg or 240 mg doses were not statistically significant for FEV_1 but were statistically significant for FVC.

Figure 10: Study 202 Change in FEV_1 from Baseline after 2-Week Treatment



Across the Phase 2 studies, all inhaled mannitol doses were well-tolerated and there was no dose-limiting toxicity. Therefore, 400 mg dose BID was defined as the optimal dose for Phase 3.

5.5.1.1 Rationale for 50 mg BID Control Dose

Each of the Phase 3 studies used inhaled mannitol 50 mg BID as a control (ten 5 mg capsules). Masking of the inhaled mannitol study medication was achieved but was recognized as not straightforward for several reasons. Use of a matched placebo inhalation powder, such as inhalation-grade lactose, was not feasible because safety data were not available. In addition, the difference in the taste of lactose compared to mannitol was identified as a concern with regards to masking since all patients had an MTT as part of the initial screening phase (described in Section 6.1.1).

Following discussion with FDA, the decision was made to employ a dose of 50 mg Bronchitol as the control in the Phase 3 clinical studies. The dose selected was supported by results from the dose-finding Study 202 (Figure 10).

6 PHASE 3 CLINICAL EFFICACY

Summary

- Three randomized, double-blind, Phase 3 studies support the benefit of Bronchitol 400 mg BID over 26 weeks in the adult CF population. With the exception of age, all three studies used similar enrollment criteria and endpoints, and patient access to, and use of, therapies to treat CF was similar.
- In Study 303, Bronchitol significantly improved FEV_1 over the 26-week treatment period in adult patients with CF with an adjusted mean difference in FEV_1 of 0.054 L (95% CI: 0.008; 0.100), p=0.020.
- When Study 303 statistical methods were applied to adults in Studies 301 and 302, improvements in FEV_1 in favor of Bronchitol were observed over the 26-week treatment period in adult patients: 0.081 L (95% CI: 0.029; 0.133) in Study 301 and 0.080 L (95% CI: 0.009; 0.150) in Study 302.
- Sensitivity analyses that account for missing data support the robustness of FEV_1 results.
- In each Phase 3 study, the percentage of patients who were FEV_1 responders at Week 26 was consistently higher in the Bronchitol group compared to control at pre-specified thresholds of 0.050 L, 0.075 L, and 0.100 L.
- Additional pulmonary function endpoints, FVC and FEF_{25-75}, showed improvements that supported the findings observed in FEV_1.
- Protocol Defined Pulmonary Exacerbation events occurred infrequently and were reported in approximately 13% and 14% of Bronchitol and control patients, respectively (Study 303). Analyses of these events showed no relevant differences between Bronchitol and control groups.
- CFQ-R respiratory domain (ie, patient assessment of symptoms) change from baseline was minimal and comparable between Bronchitol and control (0.02 and -0.56, respectively in Study 303).
- Overall, in adult patients with CF, Bronchitol demonstrated consistent and definitive improvements in lung function in three independent Phase 3 studies.

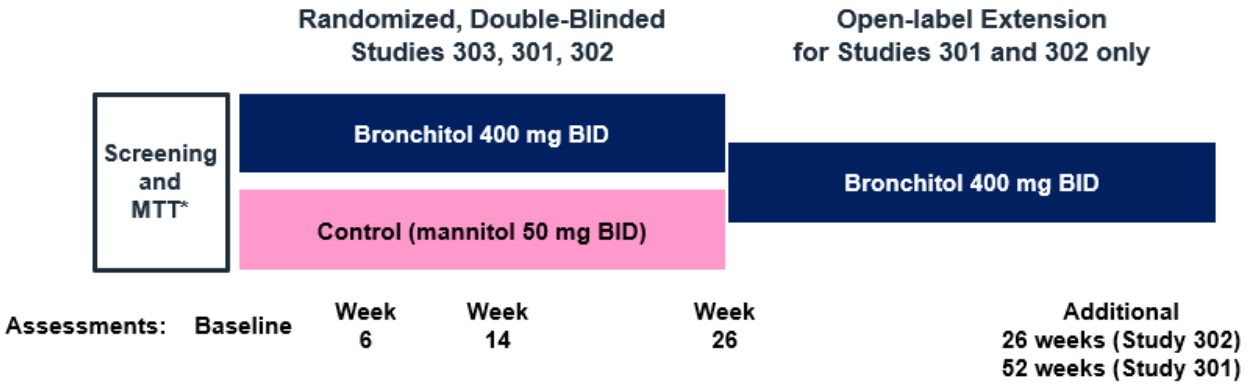
6.1 Study Design – Phase 3 Studies

Three randomized, double-blind, controlled, Phase 3 studies (Studies 301, 302, and 303) using similar design and endpoints were conducted in patients with CF to assess the efficacy and safety of Bronchitol over 26 weeks (Figure 11). Studies 301 and 302 were completed in 2010 and included both adult and pediatric patients, while Study 303 was completed in 2017 and enrolled only adult patients.

In each Phase 3 study, eligible patients were screened for airway hyperresponsiveness at the initial screening visit through performance of the MTT under medical supervision. Patients able to successfully complete the MTT were subsequently randomized to either Bronchitol 400 mg or control (inhaled mannitol 50 mg) BID.

Evaluations were made at baseline and at weeks 6, 14, and 26 during the randomized, double-blind controlled treatment phase of the studies. Study 301 also included two optional open-label extensions of 26 weeks each, for a total of up to 52 weeks of open-label experience. Study 302 included one optional 26-week open-label extension. During the open-label extensions all patients received Bronchitol 400 mg BID with visits at Weeks 38, 52, 64, and 78 in Study 301 and at Weeks 38 and 52 in Study 302.

Figure 11: Phase 3 Study Design



*Mannitol Tolerance Test (MTT) administered under medical supervision
BID=Twice Daily

6.1.1 Mannitol Tolerance Test Screening

Since patients with CF may experience airway hyperresponsiveness or bronchoconstriction following inhalation of dry powder mannitol, all Phase 3 studies included an MTT at screening. The MTT was conducted using sequential mannitol administrations and FEV_1 and SpO_2 measurement at sequential time points during the MTT. Patients with a 20% fall in FEV_1 or fall in oxygen saturation to less than 89% at any time during mannitol dose escalation or who were unable to complete the MTT for other reasons were excluded from participation.

6.1.2 Dosing and Administration

In Studies 301 and 302, patients were randomized 3:2 to Bronchitol or control. In Study 303, patients were randomized 1:1 to Bronchitol or control.

Bronchitol was administered at a dose of 400 mg BID (ten 40 mg capsules inhaled sequentially). In line with discussions with the FDA, the masked control comprised Bronchitol 50 mg BID (ten 5 mg capsules inhaled sequentially).

A bronchodilator (albuterol/salbutamol metered dose inhaler or similar) was used as premedication before inhalation of study drug. The bronchodilator could also be used in the event of post-treatment chest tightness.

6.1.3 Enrollment Criteria

With the exception of age, all three Phase 3 studies had similar inclusion and exclusion criteria, as summarized in Table 13.

The three Phase 3 studies enrolled adult patients with a diagnosis of CF with mildly to severely impaired lung function (percent predicted FEV_1 at screening of ≥30% and <90%). Patients were allowed to use background therapies, including rhDNase and inhaled antibiotics; however, the maintenance use of hypertonic saline was prohibited. Of note, Studies 301 and 302 also enrolled pediatric patients (ie, aged 6-17 years), but the proposed indication for Bronchitol is for the adult population.

Patient access to, and use of, therapies to treat CF was similar in all three studies.

Table 13: Key Inclusion/Exclusion Criteria for the Phase 3 Studies

	Study 303	Study 301	Study 302
Key Inclusion Criteria			
Age	≥18 years	≥6 years	
% Predicted FEV_1 at Screening	>40% and <90%	≥30% and <90%	≥40% and <90%
Confirmed Diagnosis of CF	Confirmed by: - Positive sweat chloride value >60 mEq/L; - And/or genotype with 2 identifiable mutations consistent with CF, accompanied by one or more clinical features consistent with the CF phenotype.	Existing diagnosis of CF; evaluated by Investigator	Confirmed by: - Positive sweat chloride value >60 mEq/L; - And/or genotype with 2 identifiable mutations consistent with CF, accompanied by one or more clinical features consistent with the CF phenotype.
Permitted Maintenance Therapies	Established antibiotics and/or rhDNase treatments [a]		
Key Exclusion Criteria			
Prohibited Therapies	Maintenance nebulized hypertonic saline within two weeks prior to randomization [b] and non-selective oral β-blockers	Nebulized hypertonic saline [c] and β-blockers	
Mannitol Tolerance Test (MTT)	Failure to successfully complete the MTT		
Medical Conditions	- Considered "terminally ill," listed for lung transplantation or had lung transplant; - Known cerebral, aortic, or abdominal aneurysm; - Uncontrolled hypertension (systolic BP >190 mmHg and/or diastolic BP >100 mHg). In the 3 months prior to screening: - Significant episode of hemoptysis (>60 mL); - Myocardial infarction; - Cerebral vascular accident; - Major ocular, abdominal, chest, or brain surgery.		

a If maintenance therapies (rhDNase and/or antibiotics) were used, these must have been established for at least 1 month prior to screening (Visit 0) and the patient should have been adherent for at least 80% of the time in the 2 weeks prior to randomization (Visit 1). Where possible the use of all concomitant medications (including rhDNase) at the start of the treatment period should have been maintained throughout the treatment period, and wherever possible, use of new concomitant medications should have been avoided.
b Patients were eligible if a 2-week wash-out for Study 303 prior to randomization was respected.
c Patients were eligible if a 4-week wash-out for Studies 301 and 302 prior to randomization was respected.
BP=Blood pressure; CF=Cystic fibrosis; FEV_1=Forced expiratory volume in 1 second; MTT=Mannitol tolerance test; rhDNase=Recombinant human deoxyribonuclease

6.1.4 Study Assessments

All three Phase 3 studies used established and widely-accepted efficacy assessments. Each study evaluated pulmonary function using the same measures (FEV_1, FVC, FEF_{25-75}). Pulmonary function has been the basis for recent pivotal trials of other therapies in patients with CF, including the change in FEV_1 as the primary efficacy endpoint.

In addition, all three Phase 3 studies evaluated pulmonary exacerbations, antibiotic use, and patient reported CF symptoms using the CFQ-R respiratory domain tool. These endpoints are summarized in Section 6.1.5.

6.1.4.1 Pulmonary Function Tests

FEV_1 was selected as the primary assessment in all three Phase 3 studies since pulmonary function is the best predictor of morbidity and mortality in patients with CF. FEV_1 is a widely accepted and established clinical efficacy endpoint in CF therapeutic studies (Yankaskas 2004, Mayer-Hamblett 2007, VanDevanter 2012). The spirometry assessment also allowed for the evaluation of changes in FVC and FEF_{25-75}.

In each Phase 3 study, spirometry assessments were performed by a trained, experienced, qualified technician, according to the American Thoracic Society/European Respiratory Society (ATS/ERS) criteria (Miller 2005) using a standardized spirometer that met the ATS/ERS guidelines. In Study 303 a central spirometry laboratory (Vitalograph) was used for central over-reading as an additional quality assurance step.

6.1.4.2 Pulmonary Exacerbations

A PDPE was defined as occurring when patients were treated with IV antibiotics for 4 or more of the following 12 signs or symptoms (Fuchs 1994):

1. Change in sputum production (volume, color, consistency);
2. Increased dyspnea;
3. New or increased hemoptysis;
4. Malaise, fatigue or lethargy;
5. Fever (>38^{o}C);
6. Anorexia or weight loss;
7. Sinus pain or tenderness;
8. Change in sinus discharge;
9. FVC or FEV_1 decreased by >10% from previous recorded value;
10. Radiographic signs indicative of pulmonary infection;
11. Increased cough;
12. Changes in physical examination of the chest.

A pulmonary exacerbation that did not meet the definition of PDPE occurred when patients had a pulmonary event treated with antibiotics (oral, IV, or inhaled).

6.1.4.3 Cystic Fibrosis Questionnaire-Revised (CFQ-R)

In Study 303 the CFQ-R respiratory domain (Appendix 11.1) was included as a secondary endpoint. The CFQ-R respiratory domain is a disease-specific symptom score assessment tool. The highest score indicated the best response and the lowest score the worst response.

6.1.5 Efficacy Endpoints

6.1.5.1 Primary Endpoint

The primary endpoint in each Phase 3 study was the change from baseline in FEV_1 over the 26-week treatment period.

6.1.5.2 Secondary Endpoints

Supportive pulmonary function secondary endpoints in each study included:

- Change from baseline percent predicted FEV_1 over the 26-week treatment period
- Change from baseline in FVC over the 26-week treatment period
- Change from baseline in FEF_{25-75} over the 26-week treatment period (post hoc in 303)

The following non-spirometry secondary endpoints were also evaluated in the three Phase 3 studies:

- Rate of PDPE
- Time to first PDPE
- Number of days of antibiotic use due to PDPE
- Number of days in hospital due to PDPE
- CFQ-R respiratory domain

6.2 Statistical Analyses

The statistical methods used in Study 303 included specific rules for the handling of missing data since that was a point of attention from Studies 301 and 302. Additionally, sensitivity analyses to further evaluate the impact of missing data on the results were clarified with the FDA as part of the Study 303 Statistical Analysis Plan.

6.2.1 Statistical Methodology Based on Study 303

To permit a comparison of results between studies, the same statistical methods and analysis population used for Study 303 were also applied to the Studies 301 and 302 (adult patients) and to the integrated analysis of the three Phase 3 studies. Results for Studies 301 and 302 in the adult population are presented with 95% CIs and p-values with the acknowledgement that these analyses were performed post hoc in the adult patients.

6.2.2 Analysis Populations

In Study 303, the ITT Set was defined as all patients who were randomized, regardless of study medication intake. In Study 303, the ITT Set included 3 patients (2 randomized to Bronchitol, 1 to control) who did not receive any study medication.

Of note, the original ITT Set definition for Study 301 and Study 302 required patients to have received at least one dose of study medication. In the re-analysis of the adult subsets in Studies 301 and 302 and in the integrated analysis presented here, the definition of ITT used for Study 303 was applied. As a result, the adult ITT Set in Study 301 and 302 re-analysis included a total of 25 additional patients (14 randomized to Bronchitol and 11 to control) who were not included in the original ITT Set because they were randomized but had not received study medication.

6.2.3 Endpoint Analyses

6.2.3.1 Primary Endpoint

The change from baseline in FEV_1 over the 26-week treatment period (measured at Weeks 6, 14, and 26) was analyzed as per the Study 303 statistical analysis plan using MMRM with treatment group, rhDNase use, pooled country, visit, treatment group-by-visit interaction, and study (only for the integrated model) as fixed effects, and baseline FEV_1 and, disease severity (% predicted FEV_1 at baseline) as covariates. The analysis included all data, regardless of adherence to or discontinuation of study medication.

6.2.3.2 Handling of missing data

Missing post-baseline FEV_1 measurements as a result of withdrawal from the study were imputed using an IUDR methodology as per Study 303 Statistical Analysis Plan. For patients who withdrew from the study due to AE, death, physician decision, or lack of efficacy, missing post-baseline FEV_1 measures were imputed using the baseline FEV_1 measurement (BOCF procedure). Missing FEV_1 measurements where the withdrawal was a result of other causes (ie, lost to follow-up, relocation, pregnancy, major protocol deviation, sponsor decision, withdrawal of consent, or other) were not imputed (and, hence, are considered as missing at random). Missing data at intermediate visits (ie, where data are available at a later visit) were not imputed.

6.2.3.3 Sensitivity Analyses

The following sensitivity analyses were performed to evaluate the impact of different data imputation strategies:

1. Pattern Mixture Model, following the same principles as the primary analysis (ie, missing not at random). Multiple imputation of missing data from the distribution of baseline values was applied to patients who withdrew from the study due to AE, death, physician decision or lack of efficacy, while multiple imputation of missing data considering the completers of the same treatment group was applied to patients withdrawing for other reasons. This approach overcomes the underestimation in variability from using a single imputation BOCF. The analysis was conducted using an analysis of covariance (ANCOVA) model.

1. Pattern Mixture Model, with multiple imputation of missing data from the distribution of baseline values for all patients who withdrew from the study regardless of the reason, using ANCOVA model for the analysis.
2. Mixed Model Repeated Measurement, without imputation of missing data (ie, under the assumption of missing at random)
3. Tipping point analysis, with multiple imputation of missing data using a regression-based approach, with increasing penalties (and different penalties for each treatment group) applied to missing data until significant difference between treatments is lost
4. Responder analysis, using logistic regression model, where a responder is defined as a patient having FEV_1 changes from baseline at Week 26 above specific thresholds (0.050 L, 0.075 L and 0.100 L), and with patients having missing Week 26 data assumed to be non-responders
5. Responder analysis for changes at Week 26, with a graphical representation of the percentage of responders using a range of possible thresholds from 0 to 0.400 L.

After submission, additional sensitivity analyses, not shown in this briefing document, were performed as requested by the FDA:

1. Pattern Mixture Model, as analysis 1 above but using a MMRM model for the analysis (in line with the primary model) instead of ANCOVA model
2. Bi-dimensional tipping point analysis with different set of penalties for each treatment group
3. Continuous Responder Analysis for changes at week 26 with thresholds from -0.200 to 0.400 L
4. Continuous Responder Analysis for changes over 26 weeks with thresholds from -0.200 to 0.400 L

6.2.3.4 Secondary Endpoints

The main analysis method used for the change from baseline in FEV_1 over the 26-week treatment period was applied to all other lung-function-related endpoints and CFQ-R respiratory domain scores, adjusting for the relevant baseline covariate.

The PDPE rate and number of days on antibiotics and in hospital due to PDPE over the 26-week treatment period were analyzed using a negative binomial model, including treatment group, rhDNase use, pooled country, and study (only for the integrated model) as fixed effects, and log-time on study as an offset variable.

The time to first PDPE was analyzed using Cox's proportional hazards regression model, including treatment group, rhDNase use, pooled country, and study (only for the integrated model) as fixed effects.

No imputation of missing data was performed for these PDPE-related endpoints. Patients who withdrew from the study prior to a PDPE occurring were considered as censored in the time to first PDPE analysis.

6.2.4 Subgroup Analyses

Subgroup analyses of the primary endpoint included disease severity (thresholds of 50, 60, and 70% predicted FEV_1 at baseline), use of rhDNase at screening, and gender.

6.3 Patient Population

6.3.1 Disposition

The adult patient disposition for the individual Phase 3 Studies and integrated population is presented in Table 14.

In Study 303, a total of 486 patients underwent MTT screening, and 454 patients (93.4%) passed the MTT. Of the patients that passed, 423 were randomized and 420 patients (99.3%) received at least 1 dose of study medication. The ITT Set for Study 303 comprised 209 patients in the Bronchitol group and 214 patients in the control group.

The majority of randomized patients in Study 303 completed the 26-week double-blind treatment (373 patients, 88.2%). In Study 303, patients who discontinued study medication were encouraged to remain in the study. A total of 34 patients (8.0%) completed the study despite having discontinued study medication. Consequently, a higher percentage of patients completed Study 303 compared to the two previous Phase 3 studies, with a balanced distribution between treatment groups (87.6% in the Bronchitol group and 88.8% in the control group).

Across the Phase 3 studies, a total of 896 adult patients underwent the MTT, and 824 of these patients (92.0%) passed the MTT. Overall, 789 adult patients (88.1%) were randomized to treatment with either Bronchitol 400 mg BID or control across the three Phase 3 studies.

A total of 28 patients withdrew from their respective study after randomization but before the administration of the first study medication (3 patients in Study 303, 19 patients in Study 301, and 6 patients in Study 302). These 28 untreated patients (16 in the Bronchitol group and 12 in the control group) were nonetheless included in the ITT set.

A total of 761 adult patients (96.5%) were treated with study drug and 616 patients (78.1%) completed the 26-week double-blind treatment. The most common reasons for study withdrawal in both treatment groups were withdrawal of consent (9.3% in the Bronchitol group and 10.0% in the control group) and AEs (10.0% in the Bronchitol group and 5.6% in the control group). All other reasons for withdrawal occurred in less than 2% of patients in either group.

Table 14: Patient Disposition During the Treatment Period in Phase 3 Studies (≥18 Years, ITT Set)

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	**Bronchitol N=124**	**Control N=85**	**Bronchitol N=97**	**Control N=60**	**Bronchitol N=430**	**Control N=359**
Randomized (ITT Set), n (%)	209 (100.0)	214 (100.0)	124 (100.0)	85 (100.0)	97 (100.0)	60 (100.0)	430 (100.0)	359 (100.0)
Prematurely withdrawn from study before study medication, n (%)	2 (1.0)	1 (0.5)	10 (8.1)	9 (10.6)	4 (4.1)	2 (3.3)	16 (3.7)	12 (3.3)
Treated (Safety Set), n (%)	207 (99.0)	213 (99.5)	114 (91.9)	76 (89.4)	93 (95.9)	58 (96.7)	414 (96.3)	347 (96.7)
Completing the DBP, n (%)	183 (87.6)	190 (88.8)	71 (57.3)	52 (61.2)	70 (72.2)	50 (83.3)	324 (75.3)	292 (81.3)
Prematurely withdrawn from study during DBP, n (%)	26 (12.4)	24 (11.2)	53 (42.7)	33 (38.8)	27 (27.8)	10 (16.7)	106 (24.7)	67 (18.7)
Prematurely discontinuing study medication, n (%)[a]	37 (17.7)	44 (20.6)	-	-	-	-	-	-
Primary Reason for Study Withdrawal, n (%)								
Consent withdrawal	12 (5.7)	13 (6.1)	18 (14.5)	17 (20.0)	10 (10.3)	6 (10.0)	40 (9.3)	36 (10.0)
Adverse event	10 (4.8)	6 (2.8)	24 (19.4)	12 (14.1)	9 (9.3)	2 (3.3)	43 (10.0)	20 (5.6)
Physician decision	0	0	5 (4.0)	1 (1.2)	2 (2.1)	1 (1.7)	7 (1.6)	2 (0.6)
Sponsor Decision	0	0	5 (4.0)	2 (2.4)	0	0	5 (1.2)	2 (0.6)
Lost to follow-up	1 (0.5)	1 (0.5)	0	0	2 (2.1)	0	3 (0.7)	1 (0.3)
Lack of efficacy	2 (1.0)	1 (0.5)	0	0	0	0	2 (0.5)	1 (0.3)
Death	0	1 (0.5)	0	0	0	0	0	1 (0.3)
Other	1 (0.5)	2 (0.9)	1 (0.8)	1 (1.2)	4 (4.1)	1 (1.7)	6 (1.3)	4 (1.1)
Primary Reason for Premature Study Medication Discontinuation, n (%) [a]								
Adverse event	20 (9.6)	18 (8.4)	-	-	-	-	-	-
Lack of efficacy	2 (1.0)	4 (1.9)	-	-	-	-	-	-
Physician decision	0	1 (0.5)	-	-	-	-	-	-

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	**Bronchitol N=124**	**Control N=85**	**Bronchitol N=97**	**Control N=60**	**Bronchitol N=430**	**Control N=359**
Pregnancy	0	1 (0.5)	-	-	-	-	-	-
Relocation	1 (0.5)	0	-	-	-	-	-	-
Other	14 (6.7)	20 (9.3)	-	-	-	-	-	-

a To minimize missing data in Study 303, patents who discontinued study medication were encouraged to remain in the study.
ITT Set: all patients randomized.
DBP=Double-blind phase; ITT=Intent-to-treat

6.3.2 Disease Characteristics

Disease characteristics in the adult patients were generally similar for all three Phase 3 studies. However, patients enrolled in Study 303 had slightly less severe disease than observed in Studies 301 and 302 (Table 15). Patients in the Phase 3 studies had mildly to severely impaired lung function at screening, with % predicted FEV_1 from ≥30 to 90%. Study 303 had more patients with % predicted FEV_1 > 70% at baseline than Studies 301 and 302 (38.8% compared to 27.3% and 31.3%, respectively).

The *P. aeruginosa* infection rate at screening was approximately 52% across the three studies and is consistent with the estimated 50 to 70% prevalence of this infection among adult patients with CF in the US (CFF Registry 2017). As shown in Table 16, patients in Study 303 also had fewer patients with *P. aeruginosa* infection (44.0%) versus those enrolled in Studies 301 and 302 (63.2% and 58.0%, respectively), in line with the observation that the percentage of CF individuals with a positive culture for *P. aeruginosa* has continued to decline over time (CFF Registry 2017).

The CFTR mutation ΔF508 is present in 85.8% of patients with CF in the US (CFF Registry 2017) and, as expected, was the most common CF mutation among patients in Studies 302 and 303 (Table 16). No CFTR genotyping was performed in Study 301.

Patient access to, and use of, therapies to treat CF was similar across the three studies, with most patients treated with rhDNase (64.0 and 64.9% in the Bronchitol and control groups, respectively in the integrated dataset).

The study populations had well-managed CF pulmonary disease. In Studies 302 and 303, more than half of the patients had not experienced a pulmonary exacerbation treated with IV antibiotics in the 12 months prior to screening, and more than 60% had not been hospitalized due to pulmonary exacerbations in the 12 months prior to screening (Table 16). These data were not collected in Study 301.

Overall, the characteristics of the patients included in the efficacy analyses are representative of the targeted adult CF population in terms disease characteristics, as well as concurrent treatments (CFF Registry 2017).

Table 15: Patient Baseline Characteristics in Phase 3 Studies (≥18 Years, ITT Set)

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	**Bronchitol N=124**	**Control N=85**	**Bronchitol N=97**	**Control N=60**	**Bronchitol N=430**	**Control N=359**
Disease Severity (FEV_1 % of Predicted Normal Value at Baseline)								
n	209	214	124	85	97	60	430	359
Mean (SD)	63.17 (15.15)	62.98 (13.65)	57.95 (15.76)	58.46 (16.98)	61.48 (15.23)	60.34 (14.47)	61.28 (15.47)	61.47 (14.72)
Median (Min, Max)	63.76 (33.6, 98.6)	63.01 (32.8, 92.1)	57.90 (26.4, 92.2)	55.37 (29.9, 92.3)	61.30 (28.2, 92.6)	57.18 (38.9, 89.9)	61.23 (26.4, 98.6)	60.43 (29.9, 92.3)
Disease Severity (% Predicted FEV1 at Baseline), n (%)								
>90%	3 (1.4)	1 (0.5)	1 (0.8)	1 (1.2)	2 (2.1)	0	6 (1.4)	2 (0.6)
>80% to 90%	32 (15.3)	27 (12.6)	7 (5.6)	11 (12.9)	9 (9.3)	6 (10.0)	48 (11.2)	44 (12.3)
>70% to 80%	41 (19.6)	38 (17.8)	24 (19.4)	15 (17.6)	20 (20.6)	12 (20.0)	85 (19.8)	65 (18.1)
>60% to 70%	39 (18.7)	56 (26.2)	27 (21.8)	10 (11.8)	22 (22.7)	8 (13.3)	88 (20.5)	74 (20.6)
>50% to 60%	43 (20.6)	46 (21.5)	26 (21.0)	19 (22.4)	21 (21.6)	13 (21.7)	90 (20.9)	78 (21.7)
>40% to 50%	41 (19.6)	40 (18.7)	18 (14.5)	16 (18.8)	14 (14.4)	20 (33.3)	73 (17.0)	76 (21.2)
≤40%	10 (4.8)	6 (2.8)	21 (16.9)	13 (15.3)	9 (9.3)	1 (1.7)	40 (9.3)	20 (5.6)

ITT Set: all patients randomized.

FEV_1=Forced expiratory volume in 1 second; ITT=Intent-to-treat; Max=Maximum, Min=Minimum, SD=Standard deviation

Table 16: Patient Disease History and Characteristics in Phase 3 Studies (≥18 Years, ITT Set)

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	**Bronchitol N=124**	**Control N=85**	**Bronchitol N=97**	**Control N=60**	**Bronchitol N=430**	**Control N=359**
Time Since Diagnosis, years								
Mean (SD)	19.5 (9.66)	20.0 (10.21)	24.2 (10.07)	24.8 (9.02)	22.3(8.87)	24.1 (9.09)	21.5 (9.80)	21.8 (9.98)
Median (Min, Max)	20.0 (0, 53)	19.0 (1, 50)	23.0 (0, 50)	24.0 (1, 46)	22.0 (0, 45)	23.5 (6, 49)	21.0 (0, 53)	21.0 (1, 50)
Age at Diagnosis, years								
Mean (SD)	7.3 (9.48)	8.6 (12.41)	5.1 (10.70)	4.3 (9.48)	4.8(8.76)	4.8 (6.96)	6.1 (9.74)	6.9 (11.17)
Median (Min, Max)	3.0 (0, 53)	4.5 (0, 63)	0.0 (0, 48)	0.0 (0, 43)	1.0(0, 34)	1.5 (0, 29)	1.0 (0, 53)	1.0 (0, 63)
CFTR Mutation, n (%)								
Both ΔF508	55 (26.3)	48 (22.4)	-	-	39 (40.2)	26 (43.3)	-	-
One ΔF508	91 (43.5)	89 (41.6)	-	-	35 (36.1)	23 (38.3)	-	-
At least 1 other known mutation	28 (13.4)	37 (17.3)	-	-	5 (5.2)	3 (5.0)	-	-
Both unknown mutations	35 (16.7)	40 (18.7)	-	-	18 (18.6)	8 (13.3)	-	-
Pulmonary Exacerbation Hospitalizations in 12 Months Before Screening, n (%)								
0	121 (57.9)	135 (63.1)	-	-	59 (60.8)	39 (65.0)	-	-
1	57 (27.3)	43 (20.1)	-	-	20 (20.6)	16 (26.7)	-	-
2	20 (9.6)	23 (10.7)	-	-	11 (11.3)	1 (1.7)	-	-
3	11 (5.3)	9 (4.2)	-	-	3 (3.1)	3 (5.0)	-	-
4	0	3 (1.4)	-	-	2 (2.1)	0	-	-
>4	0	1 (0.5)	-	-	2 (2.1)	1 (1.7)	-	-

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	**Bronchitol N=124**	**Control N=85**	**Bronchitol N=97**	**Control N=60**	**Bronchitol N=430**	**Control N=359**
Pulmonary Exacerbation Treated with IV Antibiotics in 12 Months Before Screening, n (%)								
0	109 (52.2)	120 (56.1)	-	-	53 (54.6)	37 (61.7)	-	-
1	58 (27.8)	47 (22.0)	-	-	22 (22.7)	15 (25.0)	-	-
2	28 (13.4)	32 (15.0)	-	-	15 (15.5)	4 (6.7)	-	-
3	13 (6.2)	11 (5.1)	-	-	3 (3.1)	3 (5.0)	-	-
4	1 (0.5)	3 (1.4)	-	-	2 (2.1)	0	-	-
>4	0	1 (0.5)	-	-	2 (2.1)	1 (1.7)	-	-
Previous diagnosis of CF-related bronchiectasis, n (%)	123 (58.9)	123 (57.5)	-	-	63 (64.9)	42 (70.0)	-	-
Use of rhDNase at screening, n (%)	144 (68.9)	142 (66.4)	64 (51.6)	49 (57.6)	67 (69.1)	42 (70.0)	275 (64.0)	233 (64.9)
Previous use of hypertonic saline, n (%)	118 (56.5)	112 (52.3)	-	-	-	-	-	-
Use of hypertonic saline at screening, n (%)	41 (19.6)	41 (19.2)	-	-	-	-	-	-
Presence of *Pseudomonas aeruginosa* at screening [a], n (%)	93 (44.5)	93 (43.5)	75 (60.5)	57 (67.1)	57 (58.8)	34 (56.7)	225 (52.3)	184 (51.3)

a As specified in the sputum qualitative microbiology.
ITT set: all patients randomized.
CF=Cystic fibrosis; CFTR=Cystic fibrosis transmembrane conductance regulator; ITT=Intent-to-treat; IV=Intravenous; Max=Maximum; Min=Minimum; rhDNase=Recombinant human deoxyribonuclease; SD=Standard deviation

6.3.3 Demographics

Patient demographics were similar across the three Phase 3 studies, as summarized in Table 17, and representative of the targeted adult CF population (CFF Registry 2017).

In Study 303, the majority of patients were from the US (27.4%), Ukraine (14.9%), Poland (10.4%), and Russia (9.7%).

Adult patients included in the Phase 3 studies ranged from 18 to 78 years old. Males comprised 57.9% of patients in the Bronchitol group and 51.0% of patients in the control group. The vast majority (97.8%) of patients were white, and 26.5% of patients were within the US.

Table 17: Patient Demographics in Phase 3 Studies (≥18 Years, ITT Set)

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	**Bronchitol N=124**	**Control N=85**	**Bronchitol N=97**	**Control N=60**	**Bronchitol N=430**	**Control N=359**
Age [a], Years								
Mean (SD)	26.8 (7.64)	28.6 (10.75)	29.3 (9.24)	29.0 (8.69)	27.0 (7.88)	28.8 (8.50)	27.6 (8.24)	28.7 (9.92)
Median (Min, Max)	25.0 (18, 59)	25.0 (18, 78)	26.0 (18, 56)	26.0 (18, 49)	25.0 (18, 50)	27.0 (18, 53)	25.0 (18, 59)	26.0 (18, 78)
Male/Female, n (%) [a]	117 (56.0)/ 92 (44.0)	107 (50.0)/ 107 (50.0)	73 (58.9)/ 51 (41.1)	39 (45.9)/ 46 (54.1)	59 (60.8)/ 38 (39.2)	37 (61.7)/ 23 (38.3)	249 (57.9)/ 181 (42.1)	183 (51.0)/ 176 (49.0)
Race, n (%) [a]								
White	202 (96.7)	209 (97.7)	121 (97.6)	84 (98.8)	96 (99.0)	60 (100.0)	419 (97.4)	353 (98.3)
Asian	0	0	0	1 (1.2)	0	0	0	1 (0.3)
Black or African American	4 (1.9)	2 (0.9)	0	0	1 (1.0)	0	5 (1.2)	2 (0.6)
Other	3 (1.4)	3 (1.4)	3 (2.4)	0	0	0	6 (1.4)	3 (0.8)
Geographic Region								
US	57 (27.3)	59 (27.6)	0 (0)	0 (0)	57 (58.8)	36 (60.0)	114 (26.5)	95 (26.5)
Non-US	152 (72.7)	155 (72.4)	124 (100)	85 (100)	40 (41.2)	24 (40.0)	316 (73.5)	264 (73.5)
Weight, kg [a]								
Mean (SD)	64.04 (13.11) [b]	63.93 (15.52)	66.72 (13.53)	61.28 (13.23)	64.23 (16.22)	64.03 (13.70)	64.86 (14.01) [c]	63.32 (14.72)
Median (Min, Max)	62.00 (40.7, 105.8)	61.00 (41.0, 167.5)	66.85 (33.7, 112.0)	60.20 (28.8, 96.2)	62.40 (38.9, 147.8)	61.30 (42.0, 119.8)	63.00 (33.7, 147.8)	60.87 (28.8, 167.5)
BMI [a], kg/m^2								
Mean (SD)	22.12 (3.79) [b]	22.30 (4.13)	22.85 (3.48)	22.06 (3.52)	22.33 (3.91)	22.45 (3.19)	22.38 (3.74) [c]	22.27 (3.84)
Median (Min, Max)	21.52 (15.6, 36.8)	21.46 (15.8, 47.4)	22.15 (15.8, 37.3)	21.10 (14.9, 30.7)	21.60 (15.3, 44.6)	21.75 (15.8, 33.4)	21.71 (15.3, 44.6)	21.47 (14.9, 47.4)

a At screening
b n=208
c n=429
ITT set: all patients randomized; BMI=Body mass index; ITT=Intent-to-treat; Max=Maximum; Min=Minimum; SD=Standard deviation

6.4 Efficacy Results – Phase 3 Studies

As described in Section 6.2, results for Studies 301 and 302 in the adult population are presented with 95% CIs and p-values, with the acknowledgement that these analyses were performed post hoc.

6.4.1 Primary Endpoint Results – Change from Baseline in FEV_1 over 26 Weeks

In Study 303, the adjusted mean change from baseline in FEV_1 over the 26-week treatment period was 0.063 L in the Bronchitol group compared with 0.008 L in the control group. The difference between treatments was statistically significant and in favor of Bronchitol compared to control with an adjusted mean difference (95% CI) of 0.054 L (0.008; 0.100), p=0.020.

When identical statistical methods were applied to the adult subsets from Study 301 and 302, treatment differences in favor of Bronchitol compared to control were also observed for change from baseline in FEV_1 over 26 weeks (Table 18).

In the integrated analysis, the difference between treatments was in favor of Bronchitol compared to control, with an adjusted mean difference (95% CI) of 0.067 L (0.035; 0.098), p<0.001.

Table 18: Primary Endpoint: Change from Baseline in FEV_1 over the 26-Week Treatment Period in Phase 3 Studies (≥18 years, ITT Set)

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	**Bronchitol N=124**	**Control N=85**	**Bronchitol N=97**	**Control N=60**	**Bronchitol N=430**	**Control N=359**
Baseline (L) [a]								
n [b]	209	214	124	85	97	60	430	359
Mean (SD)	2.451 (0.760)	2.379 (0.756)	2.270 (0.837)	2.104 (0.704)	2.385 (0.754)	2.295 (0.689)	2.384 (0.783)	2.300 (0.740)
Change from Baseline over the 26-week Treatment Period								
n [c]	205	212	112	76	89	59	406	347
Adjusted mean (95% CI)	0.063 (0.025; 0.100)	0.008 (-0.027; 0.044)	0.085 (0.051; 0.119)	0.003 (-0.037; 0.044)	0.071 (0.024; 0.118)	-0.009 (-0.065; 0.048)	0.073 (0.050; 0.096)	0.007 (-0.019; 0.032)
Adjusted mean difference (95% CI), p-value	0.054 (0.008; 0.100), 0.020		0.081 (0.029; 0.133), 0.002		0.080 (0.009; 0.150), 0.028		0.067 (0.035; 0.098), <0.001	

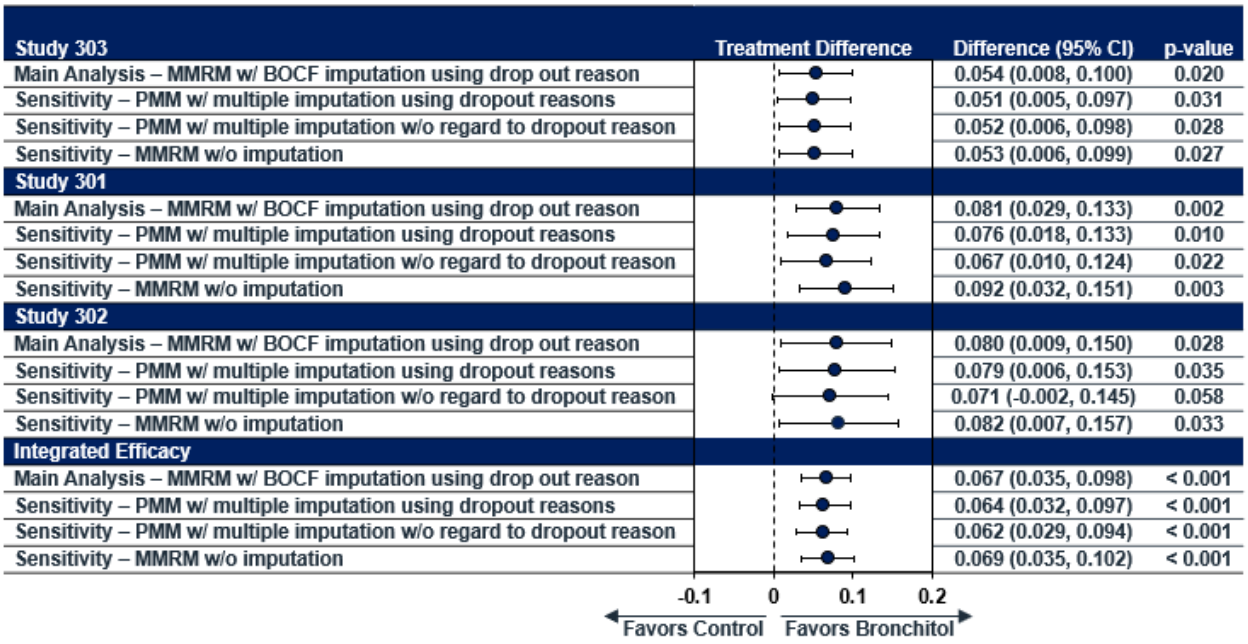
a Baseline was the pre-dose morning assessment at randomization (Week 0, Visit 1) unless the randomization assessment was missing, in which case the screening assessment was used.
b Number of patients with a non-missing baseline value.
c Number of patients included in the model. A total of 36 patients withdrawing the study (6 in Study 303, 21 in Study 301, 9 in Study 302) had no FEV_1 measure post-baseline and reasons for study withdrawal were not due to AEs, death, physician decision, or lack of efficacy. Those patients had no BOCF imputation performed and were therefore not included in the model.
Main analysis: MMRM with BOCF imputation, or no imputation, depending on drop-out reason.
BOCF=Baseline observation carried forward; CI=Confidence interval; ITT=Intent-to-treat; MMRM=Mixed model repeated measures; SD=Standard deviation

6.4.1.1 Sensitivity Analyses

6.4.1.1.1 Pattern Mixture Model and MMRM

All sensitivity analyses performed to evaluate the robustness of results confirmed the superiority of Bronchitol compared to control, with a consistent treatment effect ranging from 0.051 L to 0.053 L in Study 303 over the 26-week treatment period (Figure 12). The consistency of the treatment effect is supported by the same sensitivity analyses applied to Studies 301 and 302.

Figure 12: Change from Baseline in FEV_1 (L): Forest Plot of Main and Sensitivity Analyses over the 26-Week Treatment Period (≥18 Years, ITT Set)



BOCF=Baseline observation carried forward; CI=Confidence interval; ITT=Intent-to-treat; MMRM=Mixed model repeated measures; PMM=Pattern mixture model

6.4.1.1.2 Tipping Point

In Study 303, a tipping point analysis was performed to identify the point where there was no longer evidence of a treatment effect (ie, where the p-value for the difference between treatment groups becomes ≥0.05). The purpose of such an approach is to understand what hypothetical penalties needed to be applied to missing primary endpoint data in patients that withdrew from a trial to negate the statistically significant difference between the two treatment arms.

The tipping point analysis showed that when no penalty was applied to imputed (missing) values in the control group, a penalty of at least 0.100 L loss in FEV_1 would have been needed to be applied to the imputed (missing) values in the Bronchitol group in order for significance to be lost (Table 19). Additional penalties applied to missing data by treatment group are shown in support of the robustness of the results in Study 303. The first penalty applied to both treatment groups to impute (missing) values which would lead to a loss of statistical significance is 0.240 L.

Table 19: Tipping Point Analysis of Change from Baseline in FEV_1 in Study 303 (ITT Set)

Δ-Adjustment in the Control Group	Tipping Point Δ - Adjustment in the Bronchitol Group Giving Non-Significant Result
0	-0.100 L
-0.020 L	-0.100 L
-0.040 L	-0.120 L
-0.060 L	-0.140 L
-0.080 L	-0.140 L
-0.100 L	-0.160 L

Estimates based on analysis of covariance model including terms for treatment group, rhDNase use, pooled country, baseline FEV_1, and disease severity.
This model considered both on study drug and off study drug data, and imputed missing data after trial withdrawal following a regression-based multiple imputation approach.

In the integrated analysis, the tipping point analysis showed that when no penalty was applied to the control group, a penalty of at least 0.240 L loss in FEV_1 function would have been needed to be applied to the imputed values in the Bronchitol group for significance to be lost (Table 20). The first penalty applied to both treatment groups to impute (missing) values which would lead to a loss of statistical significance is 0.620 L.

Table 20: Tipping Point Analysis of Change from Baseline in FEV_1 in Integrated Analysis (ITT Set)

Δ-Adjustment in the Control Group	Tipping Point Δ - Adjustment in the Bronchitol Group Giving Non-Significant Result
0	-0.240 L
-0.020 L	-0.260 L
-0.040 L	-0.280 L
-0.060 L	-0.280 L
-0.080 L	-0.300 L
-0.100 L	-0.320 L

Estimates based on analysis of covariance model including terms for treatment group, rhDNase use, baseline FEV_1, disease severity and the interaction pooled country, by study ID.
This model considered both on study drug and off study drug data, and imputed missing data after trial withdrawal following a regression-based multiple imputation approach.

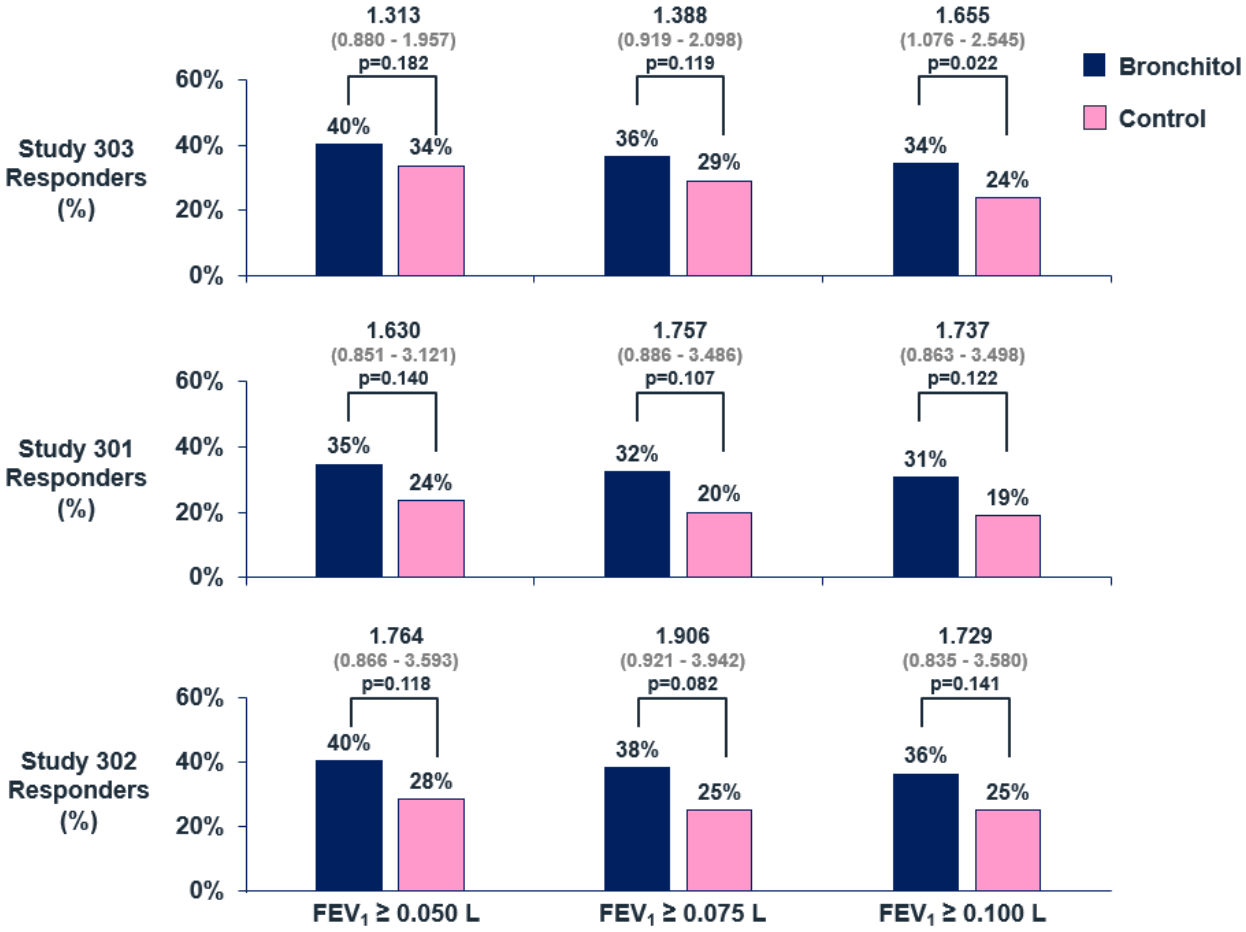
6.4.1.1.3 Responder Analyses

An additional pre-specified sensitivity analysis considered the percentage of patients responding at Week 26. At the thresholds of an improvement of 0.050 L, 0.075 L, and 0.100 L in the Study 303, the percentage of patients who were FEV_1 responders at Week 26 was higher in the Bronchitol group compared to control (Figure 13). At the threshold of 0.100 L, 34.4% of patients treated with Bronchitol were responders at 26 weeks compared with 23.8% of patients in the control group.

When identical statistical methods were applied to Studies 301 and 302, similar responder benefits were observed (Figure 13).

In addition to the pre-specified responder analysis using the three thresholds, a post hoc evaluation of the response considering additional thresholds supported the results.

Figure 13: FEV_1 Responders at Week 26 in Phase 3 Studies (≥18 years, ITT Set)



6.4.1.2 Change from Baseline FEV_1 at 6, 14, and 26 Weeks

In Study 303, Bronchitol was assessed versus control for the change from baseline in FEV_1 at weeks 6, 14, and 26 (Table 21). The adjusted mean differences between treatments were 0.060 L at Week 6, 0.061 L at Week 14, and 0.041 L at Week 26, indicating that the effect of Bronchitol on lung function was evident early and was maintained throughout the study period.

In each of the studies, Bronchitol resulted in greater change from baseline in FEV_1 at all visits, further supporting that the effect of Bronchitol on lung function was evident early and was maintained throughout the study period.

Table 21: Change from Baseline in FEV_1 (L) at Weeks 6, 14, and 26 in Phase 3 Studies (≥18 years, ITT Set)

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	**Bronchitol N=124**	**Control N=85**	**Bronchitol N=97**	**Control N=60**	**Bronchitol N=430**	**Control N=359**
Change from Baseline at Week 6								
Adjusted mean (95% CI)	0.083 (0.044; 0.123)	0.023 (-0.015; 0.062)	0.108 (0.069; 0.148)	0.047 (0.000; 0.095)	0.110 (0.061; 0.160)	0.028 (-0.032; 0.088)	0.099 (0.073; 0.124)	0.031 (0.004; 0.059)
Adjusted mean difference (95% CI), p-value	0.060 (0.010; 0.110), 0.018		0.061 (-0.002; 0.122), 0.050		0.083 (0.007; 0.158), 0.032		0.067 (0.032; 0.102), <0.001	
Change from Baseline at Week 14								
Adjusted mean (95% CI)	0.073 (0.032; 0.114)	0.012 (-0.029; 0.052)	0.070 (0.026; 0.114)	-0.011 (-0.064; 0.042)	0.055 (-0.000; 0.110)	0.010 (-0.057; 0.077)	0.071 (0.044; 0.098)	0.009 (-0.021; 0.038)
Adjusted mean difference (95% CI), p-value	0.061 (0.009; 0.114), 0.022		0.081 (0.012; 0.149), 0.021		0.045 (-0.039; 0.129), 0.294		0.063 (0.025; 0.100), 0.001	
Change from Baseline at Week 26								
Adjusted mean (95% CI)	0.032 (-0.012;0.075)	-0.009 (-0.051;0.033)	0.076 (0.032;0.120)	-0.026 (-0.080;0.027)	0.048 (-0.018;0.113)	-0.064 (-0.144;0.016)	0.050 (0.021; 0.078)	-0.020 (-0.051; 0.011)
Adjusted mean difference (95% CI), p-value	0.041 (-0.014; 0.096), 0.144		0.102 (0.034; 0.171), 0.004		0.111 (0.010; 0.212), 0.032		0.070 (0.030; 0.110), <0.001	

ITT set: all patients randomized.
Main analysis: MMRM with BOCF imputation using drop-out reason.
BOCF=Baseline observation carried forward; CI=Confidence interval; FEV_1=Forced expiratory volume in 1 second; MMRM=Mixed model repeated measures; SD=Standard deviation

6.4.2 Pulmonary Function Secondary Endpoints

Secondary endpoints assessing pulmonary function all supported the benefit of Bronchitol.

6.4.2.1 Change from Baseline in Percent Predicted FEV_1 over 26 Weeks

The percent predicted FEV_1 (%) at baseline and the adjusted changes from baseline in percent predicted FEV_1 (%) over the 26-week treatment period are presented in Table 22.

In Study 303, the difference between treatments was in favor of Bronchitol compared to control, with an adjusted mean difference (95% CI) of 1.213% (0.071; 2.355).

In Study 301 and 302, difference between treatments of adjusted mean differences between treatments were in favor of Bronchitol compared to control: 2.115% (0.763; 3.467) in Study 301; and 2.131% (0.216; 4.047) in Study 302.

In the integrated analysis the difference between treatments was in favor of Bronchitol compared to control, with an adjusted mean difference (95% CI) of 1.605% (0.798; 2.412).

Table 22: Change from Baseline in Percent Predicted FEV_1 (%) over the 26-Week Treatment Period in Phase 3 Studies (≥18 years, ITT Set)

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	Control N=214	Bronchitol N=124	Control N=85	Bronchitol N=97	Control N=60	Bronchitol N=430	Control N=359
Baseline (%) [a]								
n [b]	209	214	124	85	97	60	430	359
Mean (SD)	63.172 (15.147)	62.981 (13.651)	57.945 (15.756)	58.463 (16.978)	61.479 (15.231)	60.336 (14.470)	61.283 (15.469)	61.469 (14.722)
Change from Baseline Over the 26-week Treatment Period								
n [c]	205	212	112	76	89	59	406	347
Adjusted mean (95% CI)	1.598 (0.669; 2.527)	0.385 (-0.514;1.284)	2.211 (1.319; 3.103)	0.096 (-0.977; 1.169)	2.060 (0.788; 3.331)	-0.072 (-1.609; 1.466)	1.944 (1.349; 2.540)	0.340 (-0.319; 0.998)
Adjusted mean difference (95% CI), p-value	1.213 (0.071; 2.355), 0.037		2.115 (0.763; 3.467), 0.002		2.131 (0.216; 4.047). 0.029		1.605 (0.798; 2.412), <0.001	

a Baseline was the pre-dose morning assessment at randomization (Week 0, Visit 1) unless the randomization assessment was missing, in which case the screening assessment was used.

b Number of subjects with a non-missing baseline value.

c of patients included in the model. A total of 36 patients withdrawing from the study (6 in Study 303, 21 in Study 301, 9 in Study 302) had no FEV_1 measure post-baseline and reasons for study withdrawal were not due to AEs, death, physician decision, or lack of efficacy. Those patients had no BOCF imputation performed and were therefore not included in the model.

ITT set: all patients randomized.

Main analysis: MMRM with BOCF imputation using drop-out reason.

AE=Adverse event; BOCF=Baseline observation carried forward; CI=Confidence interval; FEV_1=Forced expiratory volume in 1 second; ITT=Intent-to-treat; MMRM=Mixed model repeated measures; SD=Standard deviation

6.4.2.2 Change from Baseline in FVC (L) over 26 Weeks

The pre-dose morning FVC at baseline and the adjusted changes from baseline in FVC over the 26-week treatment period are presented in Table 23.

In Study 303, the difference between treatments was numerically in favor of the Bronchitol group compared to control with an adjusted change from baseline in FVC of 0.040 L (95% CI: -0.012; 0.092), p=0.128.

In Studies 301 and 302 the adjusted mean differences between treatments were observed in favor of Bronchitol compared to control in Study 301 and Study 302. In the integrated analysis, the difference between treatments was also in favor of Bronchitol compared to control, with an adjusted mean difference (95% CI) of 0.070 L (0.033; 0.108).

Table 23: Change from Baseline in FVC over the 26-Week Treatment Period in Phase 3 Studies (≥18 years, ITT Set)

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	Control N=214	Bronchitol N=124	Control N=85	Bronchitol N=97	Control N=60	Bronchitol N=430	Control N=359
Baseline (L)[a]								
n[b]	209	214	124	85	97	60	430	359
Mean (SD)	3.676 (0.927)	3.576 (0.949)	3.503 (1.098)	3.227 (0.948)	3.582 (0.982)	3.506 (0.956)	3.605 (0.992)	3.482 (0.958)
Change from Baseline Over the 26-week Treatment Period								
n[c]	205	212	112	76	89	59	406	347
Adjusted mean (95% CI)	0.028 (-0.014; 0.070)	-0.012, (-0.053; 0.029)	0.093 (0.044; 0.141)	-0.014 (-0.073; 0.044)	0.084 (0.031; 0.137)	-0.016 (-0.080; 0.048)	0.065 (0.038; 0.093)	-0.005 (-0.036; 0.025)
Adjusted mean difference (95% CI), p-value	0.040 (-0.012; 0.092), 0.128		0.107 (0.033; 0.181), 0.005		0.101 (0.021; 0.180), 0.014		0.070 (0.033; 0.108), <0.001	

a Baseline was the pre-dose morning assessment at randomization (Week 0, Visit 1) unless the randomization assessment was missing, in which case the screening assessment was used.

b Number of patients with a non-missing baseline value.

c Number of subjects included in the model. A total of 36 subjects withdrawing the study (6 in Study 303, 21 in Study 301, 9 in Study 302) had no FVC measure post-baseline and reasons for study withdrawal not due to AEs, death, physician decision, or lack of efficacy. Those patients had no BOCF imputation performed and were therefore not included in the model.

ITT set: all patients randomized.

Main analysis: MMRM with BOCF imputation using drop out reason.

BOCF=Baseline observation carried forward; CI=Confidence interval; FVC=Forced vital capacity; ITT=Intent-to-treat; MMRM=Mixed model repeated measures; SD=Standard deviation

6.4.2.3 Change from Baseline in FEF_{25-75} (L/sec) over 26 Weeks

In Study 303, the difference between treatments for change from baseline in FEF_{25-75} was in favor of Bronchitol compared to control, with an adjusted mean difference (95% CI) of 0.087 L/s (0.020; 0.155) (Table 24).

In Study 301 and 302, the difference between treatments was numerically greater in the Bronchitol group compared to control.

In the integrated analysis, adjusted mean differences between treatments were also observed in favor of Bronchitol (adjusted mean difference [95% CI] of 0.079 L/s [0.030; 0.127]).

These improvements in FEF_{25-75} support the benefit of Bronchitol.

Table 24: Change from Baseline in FEF_{25-75} over the 26-Week Treatment Period in Phase 3 Studies (≥18 years, ITT Set)

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	Control N=214	Bronchitol N=124	Control N=85	Bronchitol N=97	Control N=60	Bronchitol N=430	Control N=359
Baseline (L/s)[a]								
n[b]	209	214	124	85	97	60	430	359
Mean (SD)	1.659 (1.091)	1.536 (0.970)	1.401 (0.865)	1.338 (0.803)	1.536 (0.834)	1.444 (0.913)	1.557 (0.979)	1.474 (0.925)
Change from Baseline Over the 26-week Treatment Period								
n[c]	205	212	111	76	89	59	405	347
Adjusted mean (95% CI)	0.109 (0.054; 0.164)	0.022 (-0.032; 0.075)	0.095 (0.042; 0.148)	0.029 (-0.035; 0.092)	0.053 (-0.028; 0.134)	-0.018 (-0.116; 0.080)	0.091 (0.055; 0.127)	0.012 (-0.027; 0.052)
Adjusted mean difference (95% CI), p-value	0.087 (0.020; 0.155), 0.012		0.066 (-0.015; 0.147), 0.109		0.071 (-0.051; 0.193), 0.249		0.079 (0.030; 0.127), 0.002	

a Baseline was the pre-dose morning assessment at randomization (Week 0, Visit 1) unless the randomization assessment was missing, in which case the screening (V0) assessment was used.
b Number of patients with a non-missing baseline value.
c Number of patients included in the model. A total of 36 patients withdrawing the study (6 in Study 303, 21 in Study 301, 9 in Study 302) had no FEF_{25-75} measure post-baseline and reason for study withdrawal not due to AEs, death, physician decision, or lack of efficacy. Those patients had no BOCF imputation performed and were therefore not included in the model.
ITT set: all patients randomized.
Main analysis: MMRM with BOCF imputation using drop-out reason.
BOCF=Baseline observation carried forward; CI=Confidence interval; FEF_{25-75}=Forced expiratory flow in middle half of an expiration; ITT=Intent-to-treat; MMRM=Mixed model repeated measures; SD=Standard deviation

6.4.3 Other Secondary Endpoints

6.4.3.1 Rate of PDPE

In Study 303, the majority of patients (86.6% and 86.4% in the Bronchitol and control groups, respectively) did not experience any PDPEs during the 26-week double-blind period, demonstrating the relative stability of CF pulmonary disease in the adult population evaluated. The rate of PDPE (event/patient/year) was very low and similar between treatment arm (0.26 vs 0.22).

No difference between the two treatments was observed in PDPE in Study 303, with an adjusted rate ratio of Bronchitol compared to control (95% CI) of 1.194 (0.714; 1.997) (Table 25). Different trends were observed in Study 301 and 302 but overall the rate of PDPE was similar between Bronchitol and control.

Table 25: PDPE Rate in Phase 3 Studies (≥18 years, ITT Set)

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	**Bronchitol N=124**	**Control N=85**	**Bronchitol N=97**	**Control N=60**	**Bronchitol N=430**	**Control N=359**
PDPE Rate								
n[a]	209	214	114	77	93	58	416	349
≥1 PDPE, n (%)	28 (13.4)	29 (13.6)	26 (21.0)	27 (31.8)	15 (15.5)	8 (13.3)	69 (16.0)	64 (17.8)
Total Number of PDPEs	34	29	35	37	18	8	87	74
Adjusted PDPE rate per patient per year (95% CI)	0.257 (0.163; 0.405)	0.215 (0.136; 0.341)	0.719 (0.489; 1.058)	0.995 (0.671; 1.475)	0.350 (0.205; 0.599)	0.221 (0.104; 0.471)	0.393 (0.302; 0.513)	0.388 (0.291; 0.517)
Adjusted rate ratio (95% CI) Bronchitol vs control, p-value	1.194 (0.714; 1.997), 0.499		0.723 (0.425; 1.231), 0.232		1.582 (0.681; 3.672), 0.286		1.014 (0.725; 1.420), 0.934	

a Number of patients included in the model.
ITT set: all patients randomized.
Main analysis: Negative binomial model.
CI=Confidence interval; ITT=Intent-to-treat; PDPE=Protocol defined pulmonary exacerbation

6.4.3.2 Time to First PDPE

In line with the low incidence of PDPE events noted above, time to first PDPE in Study 303, based on the Cox proportional hazards analysis, showed no difference between treatments, with hazard ratio of Bronchitol compared to control (95% CI) of 1.012 (0.602; 1.703).

Similarly, no difference between treatments was observed in Study 301 or Study 302.

6.4.3.3 Number of Days on Antibiotics due to PDPE

In Study 303, no difference between treatments was observed in the number of days on antibiotics due to PDPEs, with adjusted rate ratio of Bronchitol compared to control (95% CI) of 0.9 (0.2; 3.5).

No difference between treatments was observed in the number of days on antibiotics due to PDPEs in Studies 301 and 302.

6.4.3.4 Number of Days in Hospital due to PDPE

In Study 303, no difference between treatments was observed in the number of days in hospital due to PDPEs with adjusted rate ratio of Bronchitol compared to control (95% CI) of 1.6 (0.4; 6.2).

No difference between treatments was observed in the number of days in hospital due to PDPEs in Studies 301 and 302.

6.4.3.5 CFQ-R Respiratory Domain

In Study 303, the adjusted mean change from baseline in the CFQ-R respiratory domain score over the 26-week treatment period was 0.02 in the Bronchitol group and -0.56 the control group. No difference between treatments was observed, with an adjusted mean difference (95% CI) of 0.58 (-1.76; 2.92) (Table 26).

In Studies 301 and 302, the adjusted mean change from baseline in the CFQ-R respiratory domain score over the 26-week treatment period was a numerical decrease for both the Bronchitol group (-0.94 and -2.10 in Study 301 and 302, respectively) and the control group (-1.86 and -4.25, respectively). No difference between treatments was observed.

Table 26: Change from Baseline in CFQ-R Respiratory Domain Score over the 26-Week Treatment Period in Phase 3 Studies (≥18 years, ITT Set)

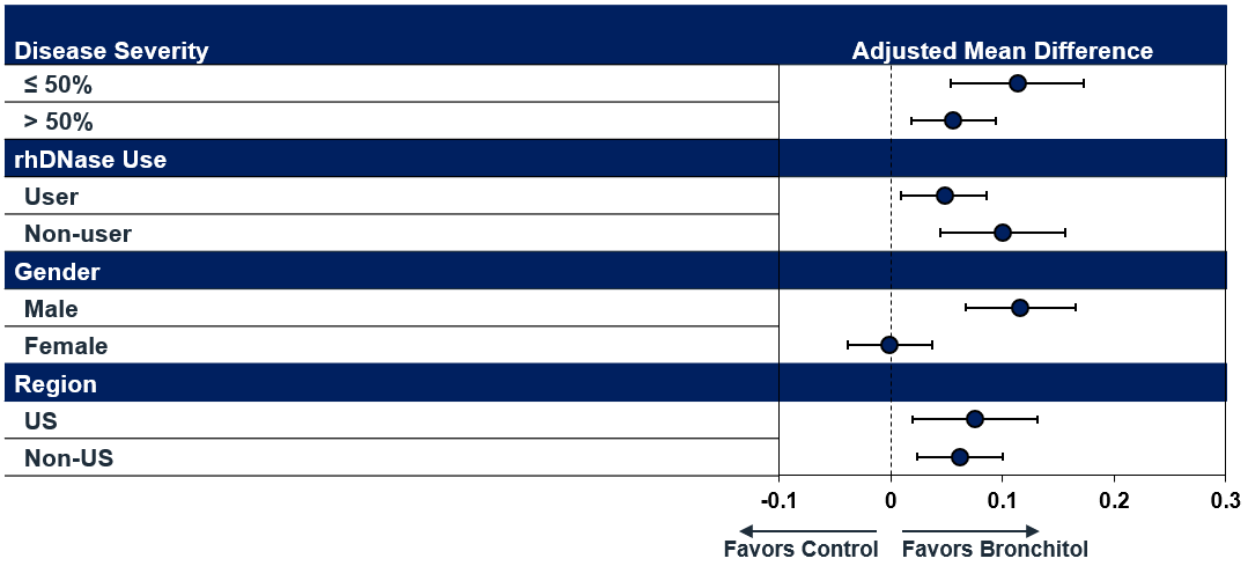
	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	**Bronchitol N=124**	**Control N=85**	**Bronchitol N=97**	**Control N=60**	**Bronchitol N=430**	**Control N=359**
Change from baseline over the 26-week treatment period								
n[a]	203	211	84	65	86	58	373	334
Adjusted Mean change from Baseline (95% CI)	0.02 (-1.91; 1.95)	-0.56 (-2.40; 1.27)	-0.94 (-3.98; 2.10)	-1.86 (-5.23; 1.50)	-2.10 (-10.57; 6.38)	-4.25 (-17.63; 9.13)	-0.19 (-1.72; 1.35)	-0.34 (-1.98; 1.29)
Adjusted mean difference (95% CI), p-value	0.58 (-1.76; 2.92), 0.627		0.92 (-3.43; 5.28), 0.676		2.15 (-13.66; 17.97), 0.748		0.16 (-1.77; 2.09), 0.871	

a Number of patients included in the model.
ITT set: all patients randomized.
Main analysis: MMRM without imputation.
CFQ-R=Cystic Fibrosis Questionnaire Revised; CI=Confidence interval; ITT=Intent-to-treat

6.4.4 Subgroup Analyses

The forest plot in Figure 14 shows the primary endpoint by pre-specified subgroups for Bronchitol and control in the integrated data from all three phase 3 studies. The subgroup analyses suggest that the effect of Bronchitol on lung function increased with disease severity (ie, with lower % predicted FEV_1 at baseline), showing a greater clinical benefit in patients with CF with more impaired lung function. The positive effect of Bronchitol on lung function was maintained in patients receiving concurrent treatment with rhDNase. Despite a greater effect observed in rhDNase non-users versus rhDNase users, the integrated analysis confirmed a significant benefit in both subgroups. A neutral effect was observed in females, with no observed differences between the treatment groups due to positive FEV_1 changes in both the Bronchitol and control groups.

Figure 14: Change in FEV_1 from Baseline over 26 Weeks by Subgroup in Integrated Phase 3 Studies (≥18 years, ITT Set)



6.5 Efficacy Conclusions

Demonstration of efficacy for Bronchitol comes from a large clinical development program including three Phase 3 studies in adult patients with CF. The characteristics of the enrolled adult patients were consistent with the expected demographic features and disease characteristics of patients with CF in the United States. The study populations had well-managed CF pulmonary disease.

Bronchitol consistently demonstrated improvements in lung function, as measured by the primary endpoint FEV_1, which was supported by improvements in other lung function parameters specifically FVC and FEF_{25-75}. The FEV_1 benefit achieved with Bronchitol was seen prospectively in adults enrolled in Study 303, and in the adult population of Studies 301 and 302, with an effect size ranging from 0.054 L to 0.081 L. The efficacy of Bronchitol in improving FEV_1 was further supported by a series of sensitivity analyses that confirmed the robustness of

the study results. In addition, the benefit of Bronchitol over control in improving FEV_1 was further supported in Study 303 by the responder analyses, where the percentage of patients classified as FEV_1 responders was numerically greater in the Bronchitol group than in the control group, reaching a statistically significant difference between treatments using the 0.100 L threshold.

PDPE events, hospitalizations, and IV antibiotic use were infrequent. Analyses of these events showed balanced results between Bronchitol and control groups over the 26-week in Study 303. There was little change in the CFQ-R respiratory domain over the 26-week treatment, and the change from baseline was comparable between treatment groups.

Overall, the efficacy results from Study 303 and from the adult population of Studies 301 and 302 support the use of Bronchitol in adult patients with CF in conjunction with standard therapies to improve pulmonary function.

7 CLINICAL SAFETY

Summary

- The safety profile of Bronchitol in adult patients with CF, when used in conjunction with standard therapies, has been well-characterized in three Phase 3 studies. The majority of the AEs observed were mild or moderate in severity, manageable, and included events that would be anticipated to occur in this patient population.
- Similar proportions of patients receiving Bronchitol or control experienced ≥1 AE (77.5% and 73.8%, respectively). The most commonly reported AE was condition aggravated (ie, pulmonary exacerbation), reported in 31.9% of Bronchitol patients and 32.9% of control patients.
- The proportions of patients with ≥1 SAE were similar in the Bronchitol (18.8%) and control (18.4%) groups.
- Permanent discontinuation of study medication due to an AE was reported by 12.3% of patients in the Bronchitol group and 8.6% in the control group. The AE most commonly responsible in the Bronchitol group was cough.
- Five AEs were designated as AEs of Special Interest: cough, pharyngolaryngeal pain, bronchospasm, hemoptysis, and pulmonary exacerbation (PT of "condition aggravated").
  - Cough (including productive cough) and pharyngolaryngeal pain were reported by more patients who received Bronchitol treatment than control. No SAEs of cough or pharyngolaryngeal pain were reported.
  - Bronchospasm was infrequent and was reported in similar proportions of patients in the Bronchitol (1.0%) and control (0.6%) groups.
  - Hemoptysis was reported in similar proportions of patients in the Bronchitol (10.4%) and control (9.5%) groups. The incidence of SAEs of hemoptysis and AEs leading to discontinuation of study drug was low (<2%) in both treatment groups.
  - Pulmonary exacerbations were reported in similar proportions of patients in the Bronchitol (31.9%) and control (32.9%) groups. SAEs of pulmonary exacerbation occurred in similar proportions of patients in both treatment groups. One patient in the control group experienced a pulmonary exacerbation with fatal outcome.
- Overall, Bronchitol 400 mg BID, used in conjunction with standard therapies, was well-tolerated by adult patients with CF.

7.1 Safety Data Integration

The safety presentation in this briefing document includes pooled safety data from the three Phase 3 studies (Studies 301, 302, and 303) considering the adult population only (ie, patients

aged ≥18 years), in alignment with the proposed indication for Bronchitol. Safety data from adult patients who received at least 1 dose of study drug were pooled to form the Safety Set.

Studies 301 and 302 also included optional open-label extensions of 52 weeks and 26 weeks, respectively. The safety findings from the open-label period are presented separately in Section 7.10.

7.2 Treatment Exposure

In the Safety Set, 761 patients were randomized and treated during the double-blind period; 414 patients were treated with Bronchitol 400 mg BID and 347 patients received inhaled mannitol 50 mg BID as control, following successful completion of the MTT (Table 27). During the double-blind treatment periods, the median duration of exposure to Bronchitol 400 mg BID was approximately 6 months and was similar for the respective control groups.

Table 27: Extent of Exposure to Inhaled Mannitol in Phase 3 Studies (≥18 years, Safety Set)

	Pooled Safety		Study 303		Study 301 [b]		Study 302 [b]	
Extent of Exposure [a]	**Bronchitol N=430**	**Control N=359**	Bronchitol N=209	Control N=214	Bronchitol N=124	Control N=85	Bronchitol N=97	Control N=60
MTT Set [b]	**896**		486		241		169	
Safety Set	**414**	**347**	207	213	114	76	93	58
Duration of Exposure (months)								
Mean (SD)	**5.10 (2.075)**	**5.39 (1.766)**	5.60 (1.721)	5.54 (1.768)	4.34 (2.377)	4.84 (1.951)	4.94 (2.110)	5.59 (1.333)
Median (Min, Max) [c]	**5.98 (0.0, 7.8)**	**6.01 (0.0, 7.8)**	6.05 (0.0, 7.8)	6.05 (0.0, 7.8)	5.80 (0.0, 7.2)	5.75 (0.3, 7.6)	5.91 (0.0, 6.7)	5.98 (0.2, 6.5)
Duration of Exposure (months), n (%)								
≤1	**40 (9.7)**	**20 (5.8)**	11 (5.3)	12 (5.6)	17 (14.9)	6 (7.9)	12 (12.9)	2 (3.4)
>1–2	**26 (6.3)**	**14 (4.0)**	7 (3.4)	8 (3.8)	15 (13.2)	5 (6.6)	4 (4.3)	1 (1.7)
>2–3	**12 (2.9)**	**8 (2.3)**	6 (2.9)	4 (1.9)	4 (3.5)	3 (3.9)	2 (2.2)	1 (1.7)
>3–4	**14 (3.4)**	**19 (5.5)**	6 (2.9)	11 (5.2)	6 (5.3)	7 (9.2)	2 (2.2)	1 (1.7)
>4–5	**6 (1.4)**	**7 (2.0)**	5 (2.4)	3 (1.4)	0 (0.0)	4 (5.3)	1 (1.1)	0 (0.0)
>5–6	**112 (27.1)**	**93 (26.8)**	34 (16.4)	35 (16.4)	37 (32.5)	29 (38.2)	41 (44.1)	29 (50.0)
>6	**204 (49.3)**	**186 (53.6)**	138 (66.7)	140 (65.7)	35 (30.7)	22 (28.9)	31 (33.3)	24 (41.4)

a Defined as duration during which adult patients received study medication (ie, Bronchitol or control).

b Only including data from adult patients.

c Included all adult patients who underwent MTT prior to randomization, regardless of the treatment to which the patient was randomized.

d Duration of exposure for adult patients who received study medication for 1 day in the DBP was rounded to 0.0 months.

BID=Twice daily; DBP=Double-blind phase; Max=Maximum; Min=Minimum; MTT=Mannitol tolerance test; SD=Standard deviation

7.3 Overview of Adverse Events

Overall, 321 patients (77.5%) in the Bronchitol group and 256 patients (73.8%) in the control group experienced ≥1 AE. The proportions of patients with severe AEs were similar in the Bronchitol group (13.3%) and the control group (12.7%) as were the proportions of patients with SAEs (18.8% and 18.4%, respectively). An overall summary of AEs (including AEs that occurred up to 28 days after permanent discontinuation of study medication) in the adult patients in Studies 301, 302, and 303 (ie, the Safety Set) is shown in Table 28.

The proportion of patients with AEs leading to permanent discontinuation of study medication was higher in the Bronchitol group (12.3%) than in the control group (8.6%). The incidence of AEs leading to permanent discontinuation of study medication was similar between the treatment groups in Study 303 (9.2% in the Bronchitol group versus 8.5% in the control group). Details of individual study results can be found in Appendix 11.2.

There was one death in the Safety Set, which was due to a severe AE of condition aggravated in a 19-year-old male patient randomized to the control group (Section 7.8).

Table 28: Summary of Adverse Events in Phase 3 Studies (≥18 years, Safety Set)

	Pooled Safety (Adult ≥ 18 Years)	
Category, n (%)	**Bronchitol N=414**	**Control N=347**
Patients with ≥1 AE	321 (77.5)	256 (73.8)
Patients with ≥1 severe AE	55 (13.3)	44 (12.7)
Patients with ≥1 serious AE	78 (18.8)	64 (18.4)
Patients with ≥1 AE leading to permanent discontinuation of study medication [a]	51 (12.3)	30 (8.6)
Patients with 1 AE leading to death	0 (0.0)	1 (0.3)

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.
AE= Adverse event

7.4 Commonly Reported Adverse Events

The most commonly reported AE was condition aggravated (PT for pulmonary exacerbation), which was reported in 31.9% of patients in the Bronchitol group and 32.9% of patients in the control group (Table 29). Other frequently reported AEs (ie, reported in ≥10% of patients in either treatment group) were cough, headache, and hemoptysis. Cough was reported in a higher percentage of patients in the Bronchitol group (15.0%) than in the control group (10.7%). Headache was reported in 10.6% of patients in the Bronchitol group and 13.8% in the control. Hemoptysis was experienced by similar proportions of patients in both treatment groups (10.4% in the Bronchitol group and 9.5% in the control group).

Table 29: Adverse Events in ≥3% of Patients in Either Treatment Group (≥18 years, Safety Set)

Preferred Term, n (%)	Pooled Safety (Adult ≥ 18 Years)	
	Bronchitol N=414	Control N=347
Patients with ≥1 AE	321 (77.5)	256 (73.8)
Condition aggravated	132 (31.9)	114 (32.9)
Cough	62 (15.0)	37 (10.7)
Headache	44 (10.6)	48 (13.8)
Hemoptysis	43 (10.4)	33 (9.5)
Nasopharyngitis	30 (7.2)	25 (7.2)
Oropharyngeal pain	29 (7.0)	15 (4.3)
Bacteria sputum identified	28 (6.8)	16 (4.6)
Upper respiratory tract infection	23 (5.6)	21 (6.1)
Pyrexia	19 (4.6)	8 (2.3)
Lower respiratory tract infection	18 (4.3)	18 (5.2)
Abdominal pain upper	13 (3.1)	13 (3.7)
Arthralgia	13 (3.1)	9 (2.6)
Vomiting	13 (3.1)	5 (1.4)
Productive cough	12 (2.9)	12 (3.5)
Sinusitis	11 (2.7)	13 (3.7)
Toothache	11 (2.7)	11 (3.2)
Abdominal pain	10 (2.4)	11 (3.2)

AE=Adverse event

7.5 Severe Adverse Events

Severe AEs were reported in 55 patients (13.3%) in the Bronchitol group and 44 patients (12.7%) in the control group (Table 30). Condition aggravated was the most frequently reported severe AE and was reported in 4.8% of patients in the Bronchitol group and 2.9% of patients in the control group. Severe AEs of cough, oropharyngeal pain (PT for pharyngolaryngeal pain), and hemoptysis occurred at low frequencies (<2% in either treatment group) and were similar among patients treated with Bronchitol and control.

Table 30: Severe Adverse Events in ≥0.5% of Patients in Either Treatment Group (≥18 years, Safety Set)

Preferred Term, n (%)	Pooled Safety (Adult ≥ 18 Years)	
	Bronchitol N=414	Control N=347
Patients with ≥1 severe AE	55 (13.3)	44 (12.7)
Condition aggravated	20 (4.8)	10 (2.9)
Cough	7 (1.7)	4 (1.2)
Oropharyngeal pain	4 (1.0)	0 (0.0)
Headache	2 (0.5)	3 (0.9)
Diarrhea	2 (0.5)	1 (0.3)
Hemoptysis	2 (0.5)	1 (0.3)
Migraine	2 (0.5)	1 (0.3)
Vomiting	2 (0.5)	1 (0.3)
Foot fracture	2 (0.5)	0 (0.0)
Abdominal pain upper	1 (0.2)	2 (0.6)
Lower respiratory tract infection	0 (0.0)	4 (1.2)
Abdominal pain	0 (0.0)	3 (0.9)
Constipation	0 (0.0)	3 (0.9)
Musculoskeletal pain	0 (0.0)	2 (0.6)
Pneumothorax	0 (0.0)	2 (0.6)
Toothache	0 (0.0)	2 (0.6)

Note: Bronchospasm not shown because reported in <0.5% of patients (1 [0.2%] Bronchitol, 0 Control).
AE= Adverse event

7.6 Adverse Events Leading to Discontinuation of Study Medication

The percentage of patients who permanently discontinued study medication due to an AE was higher in the Bronchitol group (12.3%) than in the control group (8.6%). This difference was mainly due to higher rates of patients who permanently discontinued study medication in the Bronchitol groups in Studies 301 and 302; the rates of discontinuation of study medication were similar between treatment groups in Study 303 (9.2% of patients on Bronchitol and 8.5% of patients receiving control permanently discontinued study medication due to an AE). Details on individual study results can be found in Appendix 11.2.

Cough, including productive cough, and condition aggravated (PT term for pulmonary exacerbation) were the most frequent AEs leading to permanent discontinuation of study medication. Cough was reported as an AE leading to permanent discontinuation of study medication in a higher percentage of patients in the Bronchitol group (5.3%) than in the control group (2.6%). Condition aggravated and hemoptysis were reported as AEs leading to permanent

discontinuation of study medication in similar proportions of patients in both treatment groups (Table 31).

Table 31: Adverse Events Leading to Permanent Discontinuation of Study Medication in >1 Patient in Either Treatment Group (≥18 years, Safety Set)

Preferred Term, n (%)	Pooled Safety (Adult ≥ 18 Years)	
	Bronchitol N=414	Control N=347
Patients with ≥1 AE leading permanent discontinuation of study medication [a]	51 (12.3)	30 (8.6)
Cough [b]	22 (5.3)	9 (2.6)
Condition aggravated[c]	13 (3.1)	9 (2.6)
Hemoptysis	7 (1.7)	4 (1.2)
Chest discomfort	4 (1.0)	3 (0.9)
Bronchospasm	2 (0.5)	0 (0.0)
Fatigue	2 (0.5)	0 (0.0)
Oropharyngeal pain	2 (0.5)	0 (0.0)
Headache	1 (0.2)	2 (0.6)
Wheezing	1 (0.2)	3 (0.9)

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.
b Includes PTs of "cough" and "productive cough"
c PT for pulmonary exacerbation
AE= Adverse event; PT=Preferred Term

7.7 Serious Adverse Events

The proportion of patients with ≥1 SAE was similar in the Bronchitol (18.8%) and control (18.4%) groups (Table 32). The most frequently reported SAE was condition aggravated (PT for pulmonary exacerbation), reported in 13.3% of patients in the Bronchitol group and 11.2% of patients in the control group. Hemoptysis was reported as a SAE in 1.4% of patients in the Bronchitol group and in 1.2% of patients in the control group. All other SAEs were reported in low numbers of patients in either treatment group, with no important differences in the frequency or type of SAEs between the treatment groups.

Table 32: Serious Adverse Events in >1 Patient in Either Treatment Group (≥18 years, Safety Set)

Preferred Term, n (%)	Pooled Safety (Adult ≥18 Years)	
	Bronchitol N=414	Control N=347
Patients with ≥1 serious AE	78 (18.8)	64 (18.4)
Condition aggravated	55 (13.3)	39 (11.2)
Hemoptysis	6 (1.4)	4 (1.2)
Lower respiratory tract infection	5 (1.2)	3 (0.9)
Distal intestinal obstruction syndrome	2 (0.5)	1 (0.3)
Central venous catheterization	2 (0.5)	0 (0.0)
Lung infection	1 (0.2)	2 (0.6)
Pancreatitis acute	1 (0.2)	3 (0.9)
Pneumonia	1 (0.2)	4 (1.2)
Cholelithiasis	0 (0.0)	2 (0.6)
Constipation	0 (0.0)	2 (0.6)
Intestinal obstruction	0 (0.0)	2 (0.6)
Pneumothorax	0 (0.0)	2 (0.6)

AE= Adverse event

7.8 Deaths

In the Safety Set (≥18 years), one patient enrolled in Study 303 died following a pulmonary exacerbation (PT: condition aggravated). The patient was a 19-year-old Caucasian male who was randomized to the control group. The pulmonary exacerbation occurred 219 days after administration of the first dose of study drug and the patient died 5 days later. The patient had received study medication for 216 days but had stopped treatment 3 days prior to onset of the AE because he was not feeling well. The event was considered by the Investigator as probably not related to study medication.

No deaths were reported among adult patients in Studies 301 or 302 or during the open-label extensions of these two studies.

7.9 Adverse Events of Special Interest

Cough (including productive cough), pharyngolaryngeal pain, hemoptysis, bronchospasm, and pulmonary exacerbation were identified as AESIs. Each of these events are either known to commonly occur in patients with CF or are expected based on the known pharmacologic effects of inhaled powder formulations such as Bronchitol.

7.9.1 Cough

Cough is a common occurrence in patients with CF and is also an expected AE based on the known effects of Bronchitol. In addition, the potential for local irritant activity of inhaled dry powders may be associated with cough.

The incidence of cough as an AESI (ie, reported under the PTs of "cough" and "productive cough") was higher in the Bronchitol group (16.7%) than in the control group (12.4%) (Table 33).

Severe AEs of cough were reported in 7 patients (1.7%) in the Bronchitol group and 4 patients (1.2%) in the control group. No SAEs of cough were reported in any Phase 3 study. AEs of cough led to permanent discontinuation of study medication in 5.3% of patients in the Bronchitol group and 2.6% of patients in the control group.

Table 33: Cough (≥18 years, Safety Set)

Category, n (%) [no. of events]	Pooled Safety (Adult ≥18 Years)	
	Bronchitol N=414	Control N=347
Patients with ≥1 event	69 (16.7) [86]	43 (12.4) [65]
Patients with ≥1 severe event	7 (1.7) [7]	4 (1.2) [10]
Patients with ≥1 serious event	0 (0.0) [0]	0 (0.0) [0]
Patients with ≥1 event leading to permanent discontinuation of study medication [a]	22 (5.3) [22]	9 (2.6) [9]

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.
AE=Adverse event

The occurrence of cough and productive cough may be attributed to the pharmacologic actions of Bronchitol, and thus the differences in the frequencies of these AEs between the treatment groups would be expected. In addition, inhaled mannitol usually provokes coughing after inhalation as hyperosmolarity stimulates the sensory nerves (Jia 2007). In patients with CF, cough is a natural physiological process to clear excessive secretions, and Bronchitol stimulates cough by increasing the hydration of airways and ameliorating the biophysical properties of the mucus. Therefore, the effect of Bronchitol in provoking productive coughing is recognized as clinically beneficial to patients with excessive bronchial secretions.

7.9.2 Pharyngolaryngeal Pain

When associated with administration of inhaled powders for the management of CF, pharyngolaryngeal pain is believed to be associated with the deposition of particles in the upper airways, resulting in irritation of the mucosa.

The incidence of pharyngolaryngeal pain (PT of "oropharyngeal pain") was higher in the Bronchitol group (7.0%) than in the control group (4.3%) (Table 34).

Severe AEs of pharyngolaryngeal pain were reported in 4 patients (1.0%) in the Bronchitol group and no patients in the control group. No serious AEs of pharyngolaryngeal pain were reported. Pharyngolaryngeal pain led to permanent discontinuation of study medication in 2 patients (0.5%) in the Bronchitol group and no patients in the control group.

Table 34: Pharyngolaryngeal Pain (≥18 years, Safety Set)

Category, n (%) [no. of events]	Pooled Safety (Adult ≥ 18 Years)	
	Bronchitol N=414	**Control N=347**
Patients with ≥1 event	29 (7.0) [38]	15 (4.3) [15]
Patients with ≥1 severe event	4 (1.0) [4]	0 (0.0) [0]
Patients with ≥1 serious event	0 (0.0) [0]	0 (0.0) [0]
Patients with ≥1 event leading to permanent discontinuation of study medication [a]	2 (0.5) [2]	0 (0.0) [0]

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.
Of note, Study 303 included adult patients exclusively.
AE=Adverse event

The local effects of mannitol dry powder on the upper airway may be expected to lead to oropharyngeal irritation in some patients. The occurrence of pharyngolaryngeal pain may therefore be attributed to irritation of the upper airway by Bronchitol powder and thus the differences in the frequencies of this AESI between the treatment groups are not unexpected.

7.9.3 Hemoptysis

Hemoptysis in patients with CF is attributed to airway infection and inflammation. Hemoptysis has been recognized as a common AE among CF clinical study participants, particularly in adult patients and those with more severe lung disease (Thompson 2015).

The incidence of the AE of hemoptysis was similar in the Bronchitol and control groups. Adverse events of hemoptysis were reported in 43 patients (10.4%) in the Bronchitol group and in 33 patients (9.5%) in the control group (Table 35).

Severe AEs of hemoptysis were reported in 2 patients (0.5%) in the Bronchitol group and 1 patient (0.3%) in the control group. Serious AEs of hemoptysis were reported in 6 patients (1.4%) in the Bronchitol group and 4 patients (1.2%) in the control group. Adverse events of hemoptysis led to permanent discontinuation of study medication in 7 patients (1.7%) and 4 patients (1.2%) in the Bronchitol and control groups, respectively.

Table 35: Hemoptysis (≥18 years, Safety Set)

Category, n (%) [no. of events]	Pooled Safety (Adult ≥ 18 Years)	
	Bronchitol N=414	Control N=347
Patients with ≥1 event	43 (10.4) [61]	33 (9.5) [50]
Patients with ≥1 severe event	2 (0.5) [2]	1 (0.3) [1]
Patients with ≥1 serious event	6 (1.4) [6]	4 (1.2) [4]
Patients with ≥1 event leading to permanent discontinuation of study medication [a]	7 (1.7) [7]	4 (1.2) [4]

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.
Of note, Study 303 included adult patients exclusively.
AE= Adverse event; no.=number

The incidence of hemoptysis with Bronchitol treatment in the Phase 3 studies did not exceed the expected background rates in adults with CF based upon the incidence of hemoptysis reported with placebo treatment in published clinical studies. In adult and pediatric patients with CF, the incidence of hemoptysis was 21% over 24 weeks in patients receiving placebo in a study evaluating rhDNase (Fuchs 1994) and 31% in patients receiving an aerosolized placebo in a tobramycin study (Ramsey 1999). In a 24-week study of patients with CF randomized either to tobramycin inhalation powder or tobramycin inhalation solution, the percentages of patients with hemoptysis were 13.0% and 12.4%, respectively (Konstan 2011). In a retrospective cohort study based on 8 longitudinal prospective CF clinical studies, 20% of adults and 4% of children receiving placebo experienced ≥1 hemoptysis event during the follow-up period (Thompson 2015).

7.9.4 Bronchospasm

Bronchospasm may occur following the inhalation of any medicinal product, including nebulized solutions, aerosols, or dry powders.

The incidence of bronchospasm (PTs of “bronchospasm” and “bronchial hyperreactivity”) was low among patients in the three Phase 3 studies, and no relevant differences were observed between treatment groups. Adverse events of bronchospasm were reported in 4 patients (1.0%) and 2 patients (0.6%) in the Bronchitol and control groups, respectively (Table 36).

One patient (0.2%) in the Bronchitol group experienced an AE of bronchospasm that was both severe and serious. Bronchospasm led to permanent discontinuation of study medication in 3 patients (0.7%) in the Bronchitol group and no patients in the control group.

The low rate of bronchospasm may be attributed to the use of the MTT prior to initiation of Bronchitol treatment as well as the pre-dose inhalation of a short-acting beta-agonist bronchodilator.

Table 36: Bronchospasm (≥18 years, Safety Set)

Category, n (%)[no. of events]	Pooled Safety (Adult ≥ 18 Years)	
	Bronchitol N=414	Control N=347
Patients with ≥1 event	4 (1.0) [4]	2 (0.6) [2]
Patients with ≥1 severe event	1 (0.2) [1]	0 (0.0) [0]
Patients with ≥1 serious event	1 (0.2) [1]	0 (0.0) [0]
Patients with ≥1 event leading to permanent discontinuation of study medication [a]	3 (0.7) [3]	0 (0.0) [0]

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.
AE=Adverse event; no.=number

7.9.5 Pulmonary Exacerbations

Adverse events of pulmonary exacerbation (reported under the PT of "condition aggravated") in the three Phase 3 studies were reported with similar frequencies in the Bronchitol (31.9%) and control (32.9%) groups (Table 37). Severe AEs of pulmonary exacerbation were reported in 20 patients (4.8%) in the Bronchitol group and 10 patients (2.9%) in the control group. Serious AEs of pulmonary exacerbations were reported in 55 patients (13.3%) in the Bronchitol group and 39 (11.2%) patients in the control group. Adverse events of pulmonary exacerbation led to permanent discontinuation of study medication in 13 patients (3.1%) and 9 patients (2.6%) in the Bronchitol and control groups, respectively.

Table 37: Pulmonary Exacerbation (≥18 years, Safety Set)

Category, n (%)[no. of events]	Pooled Safety (Adult ≥ 18 Years)	
	Bronchitol N=414	Control N=347
Patients with ≥1 event	132 (31.9) [190]	114 (32.9) [150]
Patients with ≥1 severe event	20 (4.8) [23]	10 (2.9) [10]
Patients with ≥1 serious event	55 (13.3) [65]	39 (11.2) [43]
Patients with ≥1 event leading to permanent discontinuation of study medication [a]	13 (3.1) [13]	9 (2.6) [9]

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.
AE= Adverse event; no.=number

The chronic infection and inflammation characteristic of CF lung disease cause a progressive decline of lung function with episodes of acute worsening of symptoms, often referred to as pulmonary exacerbations. Clinical features may include increased cough, increased sputum production, shortness of breath, chest pain, and lung function decline (Flume 2009). Pulmonary exacerbation was identified as an AESI because of its importance in the day-to-day medical management of patients with CF and as well as its impact on progression of CF lung disease.

7.10 Open-label Safety Experience

Additional safety data were collected during up to 52 weeks of open-label experience in Study 301 and up to 26 weeks in Study 302. A total of 224 adult patients received Bronchitol during these open-label extension phases in these two studies. Study 303 did not include an open-label period.

Of the 414 patients who received Bronchitol 400 mg BID and the 347 patients who received control during the double-blind treatment, 130 and 94 patients, respectively, received Bronchitol 400 mg BID during the open-label extensions of Studies 301 and 302. The median duration of exposure to Bronchitol in the open-label extensions was 6.0 months.

In the open-label extension of Studies 301 and 302, 87.1% of patients experienced ≥1 AE (Table 38). Overall, 25.4% of patients had ≥1 SAE, and 6.7% of patients had ≥1 AE leading to study withdrawal. No deaths were reported during the open-label extensions.

Table 38: Summary of Adverse Events during the Open-Label Extension Studies (≥18 years)

Category, n (%)	Open-Label Phase by Prior Randomization Group		
	Prior Bronchitol N=130	Prior Control N=94	Overall N=224
Patients with ≥1 AE	111 (85.4)	84 (89.4)	195 (87.1)
Patients with ≥1 severe AE	21 (16.2)	13 (13.8)	34 (15.2)
Patients with ≥1 serious AE	32 (24.6)	25 (26.6)	57 (25.4)
Patients with ≥1 AE leading to study withdrawal [a]	4 (3.1)	11 (11.7)	15 (6.7)
Patients with 1 AE leading to death	0 (0.0)	0 (0.0)	0 (0.0)

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.
AE= Adverse event

AESIs of cough, pharyngolaryngeal pain, hemoptysis, bronchospasm, and pulmonary exacerbation were examined during the open-label extensions of Studies 301 and 302.

The frequency of AEs of cough, pharyngolaryngeal pain, hemoptysis, and bronchospasm during open-label treatment with Bronchitol was similar to that observed during the randomized periods of the studies, while AEs of pulmonary exacerbation were reported in a higher proportion of patients (Table 39).

Table 39: Adverse Events of Special Interest in Double-Blind Treatment and the Open-Label Extensions (≥18 years)

	Phase 3 Integrated Safety Set		Open-Label Extensions
Patients with ≥1 AE	**Bronchitol N=414**	**Control N=347**	**Bronchitol N=224**
Cough [a]	69 (16.7)	43 (12.4)	29 (12.9)
Pharyngolaryngeal Pain	29 (7.0)	15 (4.3)	10 (4.5)
Hemoptysis	43 (10.4)	33 (9.5)	23 (10.3)
Bronchospasm [b]	4 (1.0)	2 (0.6)	3 (1.3)
Pulmonary Exacerbation	132 (31.9)	114 (32.9)	99 (44.2)

a Coded under PT of "cough" and "productive cough"
b Coded under PT of "bronchospasm" and "bronchial hyperreactivity"
AE=Adverse event; PT=Preferred Term

7.11 Safety Conclusions

The safety data for the adult population from the three double-blind Phase 3 studies of Bronchitol in CF, supplemented by the data from open-label use, demonstrate that daily treatment with Bronchitol is generally well-tolerated when used in conjunction with standard therapies for the management of CF. The overall rates of AEs, severe AEs, and SAEs were similar in the Bronchitol and control groups. Adverse events leading to permanent discontinuation of study medication were reported in more patients in the Bronchitol group than in control; the most frequently reported AE leading to permanent discontinuation of study medication was cough, which is common in CF and an expected effect of Bronchitol treatment. Of the five AESIs assessed, cough and pharyngolaryngeal pain occurred more often with Bronchitol than control. Bronchospasm was reported infrequently in these studies. Importantly, hemoptysis occurred in similar proportions of patients in the Bronchitol and control groups. Pulmonary exacerbation was the most frequently reported AESI and rates were similar in both treatment groups.

8 POST-MARKETING EXPERIENCE

8.1 Estimated Exposures in Patients with Cystic Fibrosis

Bronchitol is approved for marketing in Australia, in 31 countries in the EEA, Israel, Russia and Serbia as a drug for the management of CF. In all countries except Australia and Russia, approval is limited to adult patients. Bronchitol is also available on a named-patient basis in Turkey.

Post-marketing data have been collected and reviewed for the period of 02 March 2011 through 31 December 2018. Based on sales and distribution of the kits for the Bronchitol Initiation Dose Assessment, the number of exposed patients is estimated to be approximately 8,000. A total of 180 additional CF patients in 11 countries have received Bronchitol through named-patient or compassionate-use programs.

A total of 165 adverse drug reactions (ADRs) were received from 02 March 2011 to 31 December 2018. Two of the ADRs were assessed as serious and 163 were non-serious. The most frequently reported ADRs (number of reports) were cough (20), FEV_1 decreased (17), chest discomfort (17), intentional underdose (14), off-label use (7), and hemoptysis (8). The two serious ADRs reported were hemoptysis and acute kidney injury.

8.2 Observational 5-Year Safety Study of Bronchitol in UK Patients with Cystic Fibrosis

Bronchitol was licensed for use in adult CF patients in the United Kingdom (UK) in 2012. A post-authorization safety study was conducted from 01 July 2012 through 30 June 2017 using encounter data from the UK CF Registry. All adult registry patients treated with Bronchitol were matched to unexposed patients based on factors including age, BMI, and percent predicted FEV_1. Summaries of accumulating data were conducted 6-monthly for the first 3 years and annually for years 4 and 5. The outcomes of primary interest were the occurrence of hemoptysis and/or bronchospasm.

During the 5-year study period, a total of 446 patients commenced treatment with Bronchitol and 402 of these patients were compared with 947 matched unexposed patients.

The median duration of exposure to Bronchitol during the study period was 15.7 months with 315 patients still presumed to be receiving Bronchitol at the end of the study period on 30 June 2017.

Over the 5-year study period, the occurrence of hemoptysis or massive hemoptysis was similar between the two groups of patients. When treatment with IV antibiotics was used as a surrogate for pulmonary exacerbation, there was no significant difference between groups after adjustment for baseline factors. The occurrence of bronchospasm was infrequent and during the 5-year period 13 patients discontinued Bronchitol due to bronchospasm. Mortality rates among the patients treated with Bronchitol and the unexposed group did not differ over the 5-year period.

9 BENEFIT-RISK CONCLUSIONS

Progressive deterioration of pulmonary function resulting from impaired clearance of airway secretions and its consequences is the major cause of morbidity and mortality in CF. Therefore, a critical objective of CF therapy is to improve or preserve pulmonary function.

There remains an unmet need for new treatments that can improve lung function, but that do not add substantial burden for the patient given the complexity and extended duration of therapeutic interventions which patients with CF must endure on a daily basis.

Bronchitol is an easy-to-use, effective osmotic agent that improves impaired mucociliary clearance through rehydration of the airway surface liquid addressing a central feature in the pathophysiology of the disease. Bronchitol also improves airway clearance by changing the rheology of mucus and inducing productive cough. In turn, Bronchitol was demonstrated to improve lung function.

In a large Phase 3 program comprising three comparable controlled studies, Bronchitol demonstrated clinically meaningful benefits in adults with CF through consistent improvements in pulmonary function. Over the 26-week double-blind treatment period, the analyses of the changes from baseline in $FEV_{1,}$ demonstrated superiority of Bronchitol versus control in adults in each of the Phase 3 studies and in the integrated analysis. The efficacy of Bronchitol was further supported by sensitivity analyses that confirmed the robustness of the individual studies and integrated results under different assumptions concerning missing data, the analysis of change from baseline at each visit, and the responder analyses at Week 26.

Superiority of Bronchitol over control in the change from baseline in FEV_1 was also supported by other lung function parameters, specifically FVC and FEF_{25-75} in each individual study, providing a convincing significant benefit to patients with respect to pulmonary function.

Because lung function is the best predictor of morbidity and mortality in patients with CF, any significant difference between an active treatment and a control has plausible clinical relevance (EMA CF Workshop 2012). The effect observed in each of the Phase 3 studies, as well as in an integrated analysis, provides assurance that Bronchitol is associated with a definite, tangible FEV_1 benefit over control with efficacy being observed soon after initiation of treatment and maintained over 26 weeks of treatment.

Additionally, administration of Bronchitol via the DPI represents a significant improvement over nebulized therapies with respect to convenience since it can be delivered through a portable, easy-to-use, hand-held inhaler in a notably shorter time (approximately 5 minutes). Moreover, the Bronchitol delivery system requires minimal cleaning and no maintenance.

The safety profile of Bronchitol in adult patients has been well-characterized in the three Phase 3 studies. Adverse events observed were mostly mild-to-moderate and manageable, and there were no unexpected safety signals. Moreover, the adult patients enrolled and treated in the clinical studies were representative of patients expected to receive Bronchitol in marketed use with comorbidities commonly affecting patients with CF.

The safety profile of Bronchitol is also supported by 8 years of post-approval clinical experience in approximately 8,000 patients since Bronchitol was first launched in Australia in 2011.

In conclusion, Bronchitol provides a unique mechanism to improve pulmonary function, a prognostic indicator for morbidity and mortality, in adult patients with CF. Bronchitol has an acceptable safety profile and is generally well-tolerated. Data from the large clinical development program and global post-marketing experience support the positive benefit-risk profile of Bronchitol for the management of CF to improve pulmonary function in adult patients in conjunction with standard therapies.

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11 APPENDICES

11.1 Cystic Fibrosis Questionnaire – Revised Respiratory Domain

The CFQ-R respiratory domain included the following:

Indicate how you have been feeling during the past two weeks.

1. Have you been congested?
2. Have you been coughing during the day?
3. Have you had to cough up mucus?
4. Have you been wheezing?
5. Have you had trouble breathing?
6. Have you woken up during the night because you were coughing?

11.2 Phase 3 Safety Results by Individual Study

11.2.1 Overview of Adverse Events by Individual Study

Table 40: Summary of Adverse Events by Individual Phase 3 Study (≥18 Years, Safety Set)

Category, n (%)	**Study 303**		**Study 301**		**Study 302**	
	Bronchitol N=207	**Control N=213**	**Bronchitol N=114**	**Control N=76**	**Bronchitol N=93**	**Control N=58**
Patients with ≥1 AE	144 (69.6)	140 (65.7)	97 (85.1)	70 (92.1)	80 (86.0)	46 (79.3)
Patients with ≥1 severe AE	12 (5.8)	17 (8.0)	27 (23.7)	18 (23.7)	16 (17.2)	9 (15.5)
Patients with ≥1 serious AE	31 (15.0)	29 (13.6)	32 (28.1)	24 (31.6)	15 (16.1)	11 (19.0)
Patients with ≥1 AE leading to permanent discontinuation of study medication [a]	19 (9.2)	18 (8.5)	23 (20.2)	10 (13.2)	9 (9.7)	2 (3.4)
Patients with ≥1 AE leading to study withdrawal [a]	8 (3.9)	7 (3.3)	23 (20.2)	10 (13.2)	9 (9.7)	2 (3.4)
Patients with 1 AE leading to death	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.
AE= Adverse event

11.2.2 Common Adverse Events by Individual Study

Table 41: Adverse Events in ≥2% of Patients in Either Treatment Group by Individual Phase 3 Study (≥18 Years, Safety Set)

	Study 303		Study 301		Study 302	
PT, n (%)	**Bronchitol N=207**	**Control N=213**	**Bronchitol N=114**	**Control N=76**	**Bronchitol N=93**	**Control N=58**
Patients with ≥1 AE	144 (69.6)	140 (65.7)	97 (85.1)	70 (92.1)	80 (86.0)	46 (79.3)
Condition aggravated	56 (27.1)	59 (27.7)	42 (36.8)	32 (42.1)	34 (36.6)	23 (39.7)
Cough	23 (11.1)	21 (9.9)	23 (20.2)	10 (13.2)	16 (17.2)	6 (10.3)
Headache	12 (5.8)	22 (10.3)	22 (19.3)	14 (18.4)	10 (10.8)	12 (20.7)
Hemoptysis	21 (10.1)	22 (10.3)	16 (14.0)	9 (11.8)	6 (6.5)	2 (3.4)
Nasopharyngitis	12 (5.8)	10 (4.7)	14 (12.3)	12 (15.8)	4 (4.3)	3 (5.2)
Oropharyngeal pain	9 (4.3)	8 (3.8)	9 (7.9)	2 (2.6)	11 (11.8)	5 (8.6)
Bacteria sputum identified	4 (1.9)	3 (1.4)	19 (16.7)	11 (14.5)	5 (5.4)	2 (3.4)
Upper respiratory tract infection	15 (7.2)	11 (5.2)	5 (4.4)	3 (3.9)	3 (3.2)	7 (12.1)
Pyrexia	13 (6.3)	8 (3.8)	2 (1.8)	0 (0.0)	4 (4.3)	0 (0.0)
Lower respiratory tract infection	2 (1.0)	1 (0.5)	12 (10.5)	15 (19.7)	4 (4.3)	2 (3.4)
Abdominal pain upper	5 (2.4)	5 (2.3)	5 (4.4)	4 (5.3)	3 (3.2)	4 (6.9)
Arthralgia	2 (1.0)	4 (1.9)	9 (7.9)	5 (6.6)	2 (2.2)	0 (0.0)
Vomiting	2 (1.0)	2 (0.9)	7 (6.1)	3 (3.9)	4 (4.3)	0 (0.0)
Productive cough	6 (2.9)	8 (3.8)	5 (4.4)	3 (3.9)	1 (1.1)	1 (1.7)
Chest discomfort	6 (2.9)	7 (3.3)	4 (3.5)	1 (1.3)	2 (2.2)	2 (3.4)
Diarrhea	6 (2.9)	4 (1.9)	5 (4.4)	1 (1.3)	1 (1.1)	3 (5.2)
Sinusitis	5 (2.4)	9 (4.2)	2 (1.8)	1 (1.3)	4 (4.3)	3 (5.2)
Toothache	3 (1.4)	7 (3.3)	6 (5.3)	2 (2.6)	2 (2.2)	2 (3.4)
Viral upper respiratory tract infection	10 (4.8)	6 (2.8)	0 (0.0)	1 (1.3)	1 (1.1)	0 (0.0)
Abdominal pain	4 (1.9)	7 (3.3)	1 (0.9)	3 (3.9)	5 (5.4)	1 (1.7)
Rhinitis	8 (3.9)	4 (1.9)	0 (0.0)	2 (2.6)	2 (2.2)	0 (0.0)
Nausea	5 (2.4)	5 (2.3)	3 (2.6)	3 (3.9)	1 (1.1)	2 (3.4)
Wheezing	6 (2.9)	4 (1.9)	2 (1.8)	3 (3.9)	1 (1.1)	1 (1.7)
Nasal congestion	5 (2.4)	5 (2.3)	0 (0.0)	1 (1.3)	3 (3.2)	1 (1.7)
Back pain	0 (0.0)	3 (1.4)	5 (4.4)	5 (6.6)	2 (2.2)	1 (1.7)
Fatigue	2 (1.0)	5 (2.3)	4 (3.5)	1 (1.3)	1 (1.1)	3 (5.2)

PT, n (%)	Study 303		Study 301		Study 302	
	Bronchitol N=207	**Control N=213**	**Bronchitol N=114**	**Control N=76**	**Bronchitol N=93**	**Control N=58**
Rash	2 (1.0)	2 (0.9)	3 (2.6)	3 (3.9)	2 (2.2)	2 (3.4)
Influenza	3 (1.4)	5 (2.3)	1 (0.9)	1 (1.3)	2 (2.2)	3 (5.2)
Constipation	2 (1.0)	2 (0.9)	4 (3.5)	4 (5.3)	0 (0.0)	2 (3.4)
Rhinorrhea	1 (0.5)	4 (1.9)	4 (3.5)	2 (2.6)	1 (1.1)	2 (3.4)
Dizziness	0 (0.0)	4 (1.9)	1 (0.9)	1 (1.3)	0 (0.0)	2 (3.4)
Pneumonia	1 (0.5)	4 (1.9)	0 (0.0)	1 (1.3)	0 (0.0)	2 (3.4)

Of note, in Study 303, all events of hemoptysis were reported as AESIs while in Studies 301 and 302, some events were reported as AEs and some as part of pulmonary exacerbations.
AE=Adverse event; AESI=Adverse event of special interest; PT=Preferred Term

11.2.3 Severe Adverse Events by Individual Study

Table 42: Severe Adverse Events in ≥0.5% of Patients in Either Treatment Group by Individual Phase 3 Study (≥18 Years, Safety Set)

PT, n (%)	Study 303		Study 301		Study 302	
	Bronchitol N=207	Control N=213	Bronchitol N=114	Control N=76	Bronchitol N=93	Control N=58
Patients with ≥1 severe AE	12 (5.8)	17 (8.0)	27 (23.7)	18 (23.7)	16 (17.2)	9 (15.5)
Condition aggravated	6 (2.9)	4 (1.9)	9 (7.9)	5 (6.6)	5 (5.4)	1 (1.7)
Cough	0 (0.0)	0 (0.0)	6 (5.3)	4 (5.3)	1 (1.1)	0 (0.0)
Oropharyngeal pain	1 (0.5)	0 (0.0)	2 (1.8)	0 (0.0)	1 (1.1)	0 (0.0)
Headache	0 (0.0)	1 (0.5)	1 (0.9)	2 (2.6)	1 (1.1)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (1.1)	1 (1.7)
Hemoptysis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	2 (2.2)	0 (0.0)
Migraine	1 (0.5)	0 (0.0)	1 (0.9)	1 (1.3)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	2 (1.8)	1 (1.3)	0 (0.0)	0 (0.0)
Foot fracture	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	1 (1.1)	1 (1.7)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.9)	0 (0.0)	1 (1.7)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.6)	0 (0.0)	1 (1.7)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.6)	0 (0.0)	1 (1.7)
Musculoskeletal pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.7)
Pneumothorax	0 (0.0)	1 (0.5)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)
Toothache	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)

AE=Adverse event; PT=Preferred Term

11.2.4 Serious Adverse Events by Individual Studies

Table 43: Serious Adverse Events in >1 Patient in Either Treatment Group by Individual Phase 3 Study (≥18 Years, Safety Set)

	Study 303		Study 301		Study 302	
SOC, PT, n (%)	**Bronchitol N=207**	**Control N=213**	**Bronchitol N=114**	**Control N=76**	**Bronchitol N=93**	**Control N=58**
Patients with ≥1 serious AE	31 (15.0)	29 (13.6)	32 (28.1)	24 (31.6)	15 (16.1)	11 (19.0)
General Disorders and Administration Site Conditions	**20 (9.7)**	**15 (7.0)**	**22 (19.3)**	**17 (22.4)**	**13 (14.0)**	**7 (12.1)**
Condition aggravated	20 (9.7)	15 (7.0)	22 (19.3)	17 (22.4)	13 (14.0)	7 (12.1)
Infections and Infestations	**7 (3.4)**	**8 (3.8)**	**5 (4.4)**	**4 (5.3)**	**0 (0.0)**	**2 (3.4)**
Lower respiratory tract infection	1 (0.5)	0 (0.0)	4 (3.5)	2 (2.6)	0 (0.0)	1 (1.7)
Pneumonia	1 (0.5)	2 (0.9)	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.7)
Lung infection	1 (0.5)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders	**2 (1.0)**	**4 (1.9)**	**6 (5.3)**	**2 (2.6)**	**1 (1.1)**	**1 (1.7)**
Hemoptysis	1 (0.5)	3 (1.4)	4 (3.5)	1 (1.3)	1 (1.1)	0 (0.0)
Pneumothorax	0 (0.0)	1 (0.5)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders	**3 (1.4)**	**3 (1.4)**	**2 (1.8)**	**3 (3.9)**	**1 (1.1)**	**3 (5.2)**
Pancreatitis acute	1 (0.5)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Distal intestinal obstruction syndrome	1 (0.5)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (1.7)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.6)	0 (0.0)	0 (0.0)
Intestinal obstruction	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.7)
Surgical and Medical Procedures	**0 (0.0)**	**0 (0.0)**	**4 (3.5)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Central venous catheterization	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatobiliary Disorders	**0 (0.0)**	**2 (0.9)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Cholelithiasis	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AE= Adverse event; PT=Preferred Term; SOC=System Organ Class

11.2.5 Adverse Events Leading to Discontinuation by Individual Study

Table 44: Adverse Events Leading to Permanent Discontinuation of Study Medication in > 1 Patient in Either Treatment Group by Individual Phase 3 Study (≥18 Years, Safety Set)

SOC, PT, n (%)	**Study 303**		**Study 301**		**Study 302**	
	Bronchitol N=207	**Control N=213**	**Bronchitol N=114**	**Control N=76**	**Bronchitol N=93**	**Control N=58**
Patients with ≥1 AE leading to permanent discontinuation of study medication [a]	19 (9.2)	18 (8.5)	23 (20.2)	10 (13.2)	9 (9.7)	2 (3.4)
Respiratory, Thoracic and Mediastinal Disorders	**9 (4.3)**	**12 (5.6)**	**18 (15.8)**	**6 (7.9)**	**8 (8.6)**	**0 (0.0)**
Cough	5 (2.4)	5 (2.3)	11 (9.6)	4 (5.3)	5 (5.4)	0 (0.0)
Hemoptysis	1 (0.5)	4 (1.9)	5 (4.4)	0 (0.0)	1 (1.1)	0 (0.0)
Wheezing	1 (0.5)	1 (0.5)	0 (0.0)	2 (2.6)	0 (0.0)	0 (0.0)
Bronchospasm	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Obstructive airways disorder	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Oropharyngeal pain	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (1.1)	0 (0.0)
General Disorders and Administration Site Conditions	**9 (4.3)**	**9 (4.2)**	**6 (5.3)**	**2 (2.6)**	**3 (3.2)**	**1 (1.7)**
Condition aggravated	7 (3.4)	6 (2.8)	5 (4.4)	2 (2.6)	1 (1.1)	1 (1.7)
Chest discomfort	2 (1.0)	3 (1.4)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	1 (0.5)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous System Disorders	**1 (0.5)**	**2 (0.9)**	**0 (0.0)**	**1 (1.3)**	**1 (1.1)**	**0 (0.0)**
Headache	0 (0.0)	1 (0.5)	0 (0.0)	1 (1.3)	1 (1.1)	0 (0.0)
Migraine	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.

AE=Adverse event; PT=Preferred Term; SOC=System Organ Class

11.2.6 AESI Cough by Individual Study

Table 45: Cough by Individual Phase 3 Study (≥18 Years, Safety Set)

Category, n (%) [event]	**Study 303**		**Study 301**		**Study 302**	
	Bronchitol N=207	**Control N=213**	**Bronchitol N=114**	**Control N=76**	**Bronchitol N=93**	**Control N=58**
Patients with ≥1 event	27 (13.0) [32]	25 (11.7) [34]	26 (22.8) [36]	12 (15.8) [22]	16 (17.2) [18]	6 (10.3) [9]
Patients with ≥1 severe event	0 (0.0) [0]	0 (0.0) [0]	6 (5.3) [6]	4 (5.3) [10]	1 (1.1) [1]	0 (0.0) [0]
Patients with ≥1 serious event	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Patients with ≥1 event leading to permanent discontinuation of study medication [a]	6 (2.9) [6]	5 (2.3) [5]	11 (9.6) [11]	4 (5.3) [4]	5 (5.4) [5]	0 (0.0) [0]

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.
Of note, Study 303 included adult patients exclusively.
AE=Adverse event

11.2.7 AESI Pharyngolaryngeal Pain by Individual Study

Table 46: Pharyngolaryngeal Pain by Individual Phase 3 Study (≥18 Years, Safety Set)

Category, n (%) [event]	**Study 303**		**Study 301**		**Study 302**	
	Bronchitol N=207	**Control N=213**	**Bronchitol N=114**	**Control N=76**	**Bronchitol N=93**	**Control N=58**
Patients with ≥1 event	9 (4.3) [10]	8 (3.8) [8]	9 (7.9) [17]	2 (2.6) [2]	11 (11.8) [11]	5 (8.6) [5]
Patients with ≥1 severe event	1 (0.5) [1]	0 (0.0) [0]	2 (1.8) [2]	0 (0.0) [0]	1 (1.1) [1]	0 (0.0) [0]
Patients with ≥1 serious event	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Patients with ≥1 event leading to permanent discontinuation of study medication [a]	0 (0.0) [0]	0 (0.0) [0]	1 (0.9) [1]	0 (0.0) [0]	1 (1.1) [1]	0 (0.0) [0]

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.
Of note, Study 303 included adult patients exclusively.
AE=Adverse event

11.2.8 AESI Hemoptysis by Individual Study

Table 47: Hemoptysis by Individual Phase 3 Study (≥18 Years, Safety Set)

Category, n (%) [event]	**Study 303**		**Study 301**		**Study 302**	
	Bronchitol N=207	**Control N=213**	**Bronchitol N=114**	**Control N=76**	**Bronchitol N=93**	**Control N=58**
Patients with ≥1 event	21 (10.1) [28]	22 (10.3) [36]	16 (14.0) [25]	9 (11.8) [10]	6 (6.5) [8]	2 (3.4) [4]
Patients with ≥1 severe event	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [1]	2 (2.2) [2]	0 (0.0) [0]
Patients with ≥1 serious event	1 (0.5) [1]	3 (1.4) [3]	4 (3.5) [4]	1 (1.3) [1]	1 (1.1) [1]	0 (0.0) [0]
Patients with ≥1 event leading to permanent discontinuation of study medication [a]	1 (0.5) [1]	4 (1.9) [4]	5 (4.4) [5]	0 (0.0) [0]	1 (1.1) [1]	0 (0.0) [0]

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.
Of note, Study 303 included adult patients exclusively.
AE=Adverse event

11.2.9 AESI Bronchospasm by Individual Study

Table 48: Bronchospasm by Individual Phase 3 Study (≥18 Years, Safety Set)

Category, n (%) [event]	**Study 303**		**Study 301**		**Study 302**	
	Bronchitol N=207	**Control N=213**	**Bronchitol N=114**	**Control N=76**	**Bronchitol N=93**	**Control N=58**
Patients with ≥1 event	1 (0.5) [1]	2 (0.9) [2]	2 (1.8) [2]	0 (0.0) [0]	1 (1.1) [1]	0 (0.0) [0]
Patients with ≥1 severe event	0 (0.0) [0]	0 (0.0) [0]	1 (0.9) [1]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Patients with ≥1 serious event	0 (0.0) [0]	0 (0.0) [0]	1 (0.9) [1]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Patients with ≥1 event leading to permanent discontinuation of study medication [a]	1 (0.5) [1]	0 (0.0) [0]	2 (1.8) [2]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.
Of note, Study 303 included adult patients exclusively.
AE=Adverse event

11.2.10AESI Pulmonary Exacerbation by Individual Study

Table 49: Pulmonary Exacerbation by Individual Phase 3 Study (≥18 Years, Safety Set)

Category, n (%) [event]	**Study 303**		**Study 301**		**Study 302**	
	Bronchitol N=207	**Control N=213**	**Bronchitol N=114**	**Control N=76**	**Bronchitol N=93**	**Control N=58**
Patients with ≥1 event	56 (27.1) [84]	59 (27.7) [75]	42 (36.8) [59]	32 (42.1) [45]	34 (36.6) [47]	23 (39.7) [30]
Patients with ≥1 severe event	6 (2.9) [6]	4 (1.9) [4]	9 (7.9) [11]	5 (6.6) [5]	5 (5.4) [6]	1 (1.7) [1]
Patients with ≥1 serious event	20 (9.7) [25]	15 (7.0) [15]	22 (19.3) [26]	17 (22.4) [21]	13 (14.0) [14]	7 (12.1) [7]
Patients with ≥1 event leading to permanent discontinuation of study medication [a]	7 (3.4) [8]	6 (2.8) [6]	5 (4.4) [5]	2 (2.6) [2]	1 (1.1) [1]	1 (1.7) [1]

a In Studies 301 and 302, all AEs reported as leading to study withdrawal were considered as AEs leading to permanent discontinuation of study medication.
Of note, Study 303 included adult patients exclusively.
AE=Adverse event