Response to Clarification request: Cystic Fibrosis – mannitol

Section A: PRIORITY QUESTIONS

A1. Please provide the complete clinical study reports for the trials 301 and 302.

The clinical study reports for trials DPM-CF-301 and DPM-CF-302 are provided (c.f., zipped folders CF301 CSR and CF302 CSR).

A2. Please also provide complete clinical study reports for the trials 201, 202 and Robinson 1999.

The clinical study reports for trials DPM-CF-201 and DPM-CF-202 (c.f., zipped folders CF201 CSR and CF202 CSR) and the article Robinson 1999 are provided. The Robinson study was not sponsored by Pharmaxis and all study data resides with the investigator.

A3. Please provide the latest information regarding the license indication that you have available

The EMA process is still ongoing; an oral hearing with CHMP is likely to take place in May 2011. The European Marketing Authorisation Application (MAA) seeks to gain regulatory approval for Bronchitol as a: "treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to rhDNase, and in adults ineligible, intolerant, or inadequately responsive to rhDNase"[1].

Bronchitol was approved for registration in Australia on 2nd March 2011. In Australia, Bronchitol is indicated for: "the treatment of CF in both paediatric and adult populations six years and above, as either an add-on therapy to dornase alpha, or in patients intolerant to, or inadequately responsive to dornase alpha".

A4. According to the expected license indication, there are two interventions for two different populations:

- Mannitol with rhDNase for all adult CF patients; and
- Mannitol alone for adult CF patients who are ineligible, intolerant or inadequately responsive to rhDNase.

Please could you clarify:

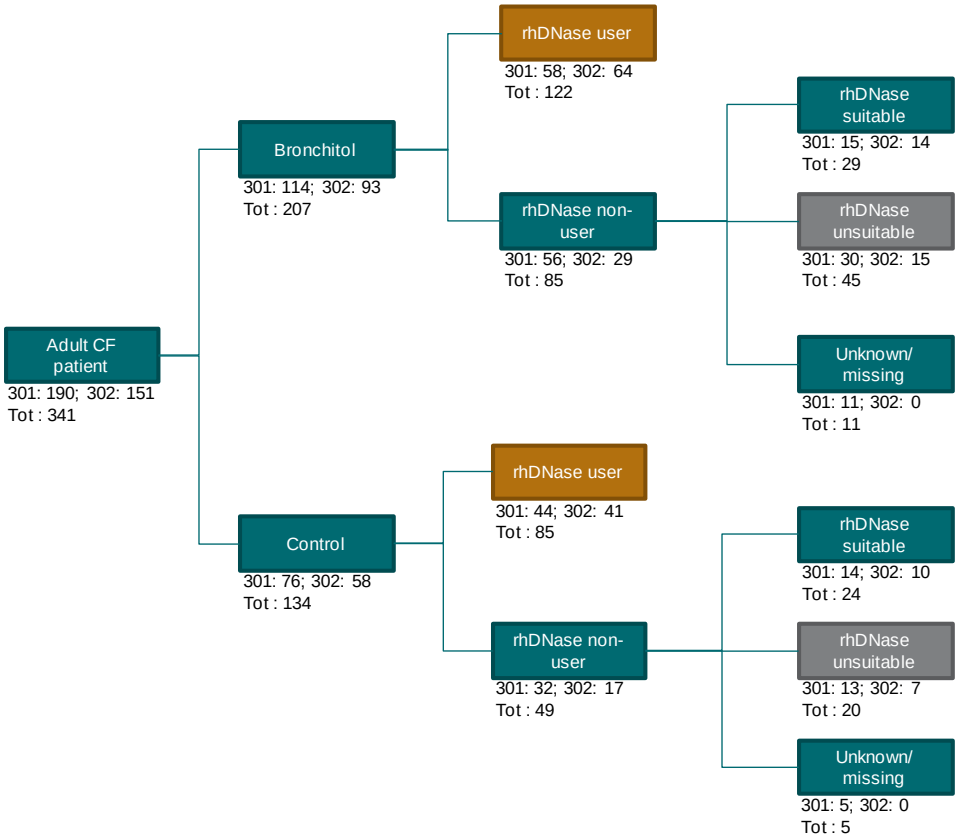
[1] The indication granted to Bronchitol is: "Bronchitol is indicated for the treatment of cystic fibrosis in adults aged 18 years and above as an add-on therapy to best standard of care".

- Why are there no separate data/analyses for mannitol alone in CF patients who are ineligible, intolerant or inadequately responsive to rhDNase?

  Studies DPM-CF-301 & 302 were originally planned to analyse rhDNase users and rhDNase non-users separately, in addition to the overall population. Although mechanistically there is no reason why the subset of rhDNase unsuitable patients would be expected to differ in terms of efficacy from the broader rhDNase non-user population, the rhDNase unsuitable population in the DPM-CF-301 study was identified post-hoc, after randomisation. These patients were identified prospectively in the DPM-CF-302 study. At the time of submission of this dossier, the rhDNase unsuitable population was considered too small for reliable analysis of effect of mannitol in the changes of FEV_1 or on protocol defined pulmonary exacerbation (PDPE) rate and incidence (see Figure 1). However, this analysis has now been conducted for each phase III study and for the pooled adult rhDNAse unsuitable population. This analysis is presented below.

  Please note that the patient distribution regarding rhDNase use in the mannitol trials may not be representative of the clinical practice setting. The proportion of CF adults rhDNase non-users in clinical practice is much higher than that observed in the mannitol studies.

  Figure 1. Proportion of adults ineligible, intolerant or inadequately responsive to rhDNase in the pivotal studies

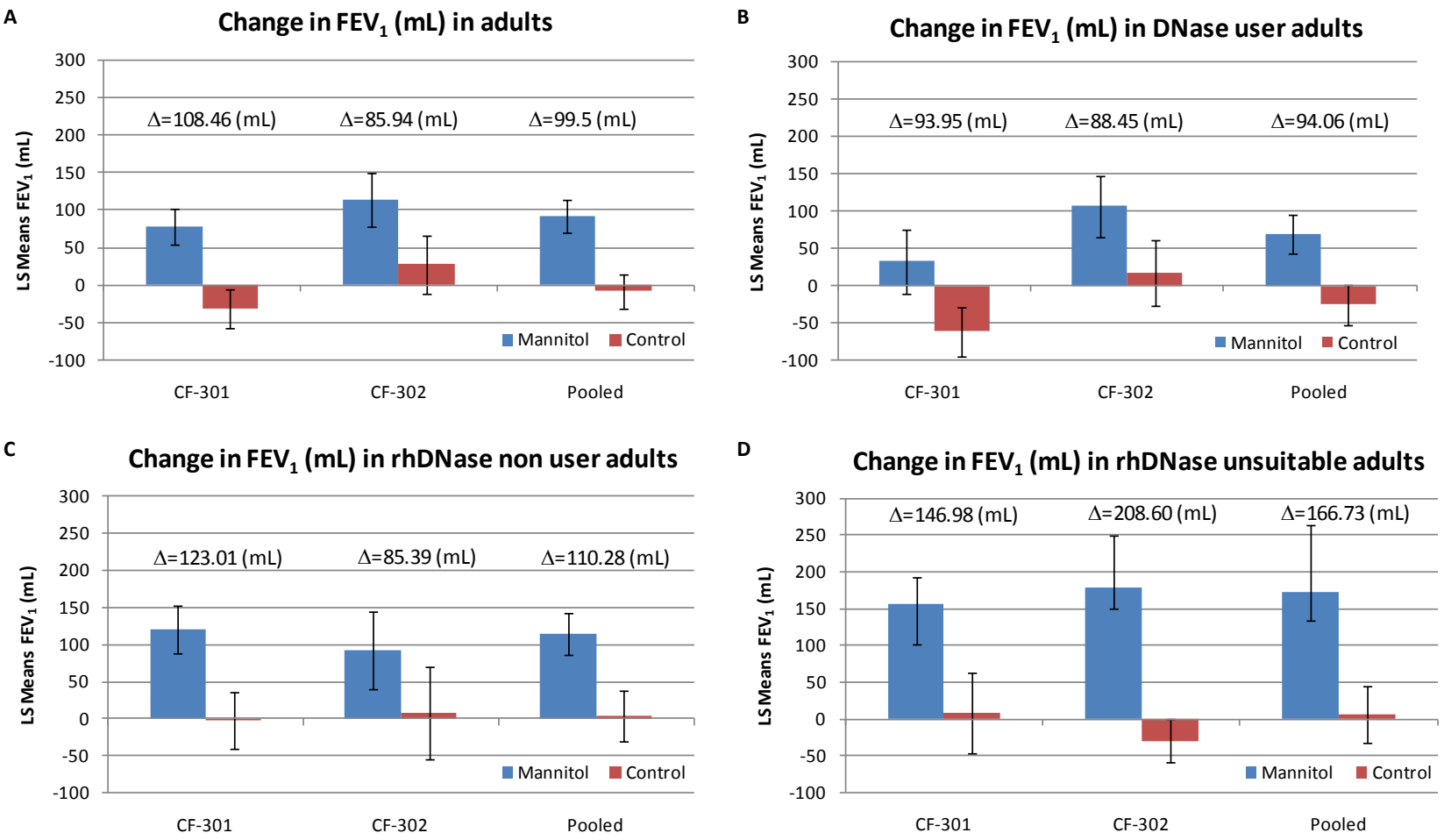


Note: rhDNase unsuitable refers to patients that are ineligible, intolerant or inadequately responsive to rhDNase.

As observed in Figure 2, changes in FEV_1 (mL) from baseline tended to be numerically higher in rhDNase unsuitable adults compared to the overall adult population and other rhDNase subgroups in the phase III trials. Among the adult subpopulation of patients for whom rhDNase is unsuitable, the absolute change in FEV_1 for mannitol versus control was statistically significant (166.73 mL, p = 0.004, N=65) for the pooled phase III adult population.

In the individual phase III studies, the absolute change in FEV_1 for mannitol versus control in rhDNase unsuitable adults was statistically significant in DPM-CF-301 (p = 146.98 mL, 0.020, N=43). The effect size was even larger in DPM-CF-302 (208.6 mL, p = 0.061, N=22), but the smaller sample size prevents definite conclusions about significance.

Figure 2. Changes in FEV_1 (mL) for (A) all adults, (B) DNase user adults, (C) DNase non user adults and (D) adults ineligible, intolerant or inadequately responsive to rhDNase



Note: Δ refers to the difference between Bronchitol and Control

As presented in Table 1 and Table 2, although not powered to examine exacerbations, the pooled data in adult rhDNase non-users and rhDNase unsuitable strongly supports the statistically significant reduction in PDPE incidence and rate observed in the overall pooled population. The rate of PDPE presented in Table 2 corresponds to the average number of PDPE experienced per patient year. Like for the model, these values were not corrected for patient's baseline PDPE rate.

Table 1. PDPE incidence in adults according to their rhDNase status

	DPM-CF-301				DPM-CF-302				Pooled population			
	Control		Mannitol		Control		Mannitol		Control		Mannitol	
rhDNAse status	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Unsuitable*	4	30.77%	5	16.67%	3	42.86%	2	13.33%	7	35.00%	7	15.56%
Non user	7	36.84%	5	19.23%	1	10.00%	1	7.14%	8	27.59%	6	15.00%
User	16	36.36%	16	27.59%	4	9.76%	12	18.75%	20	23.53%	28	22.95%

*Adults ineligible, intolerant or inadequately responsive to rhDNase.

Table 2. PDPE rate per year in adults according to their rhDNase status

	DPM-CF-301				DPM-CF-302				Pooled population			
	Control		Mannitol		Control		Mannitol		Control		Mannitol	
rhDNAse status	**N**	**Mean±SD (range)**	**N**	**Mean±SD (range)**	**N**	**Mean±SD (range)**	**N**	**Mean±SD (range)**	**N**	**Mean±SD (range)**	**N**	**Mean±SD (range)**
Unsuitable*	13	0.64±1.00 (0 – 2.15)	30	0.41±1.11 (0 – 4.34)	7	0.86±1.08 (0 – 2.15)	15	0.26±0.68 (0 – 1.97)	20	0.72±1.01 (0 – 2.15)	45	0.36±0.91 (0 – 4.34)
Non user	19	1.62±2.72 (0 – 9.6)	26	0.99±2.30 (0 – 9.48)	10	0.19±0.61 (0 – 1.93)	14	0.14±0.52 (0 – 1.93)	29	1.13±2.31 (0 – 9.6)	40	0.69±1.91 (0 – 8.48)
User	44	1.58±2.70 (0– 11.06)	58	1.41±2.69 (0 – 10.42)	41	0.19±0.58 (0– 2.07)	64	0.83±2.51 (0 – 16.58)	85	0.91±2.10 (0– 11.06)	122	1.09±2.60 (0 – 16.58)

*Adults ineligible, intolerant or inadequately responsive to rhDNase.

- Why is there no separate attempt to perform an indirect comparison (versus hypertonic saline) for these two populations/comparisons?

  For any meaningful indirect comparison to be undertaken, studies would need to be similar in terms of length, age range, disease severity, and concomitant medication use. As discussed below in A5, after a systematic literature review, comparison with hypertonic saline was not deemed to be feasible for the adult population or for adult subgroups (e.g., adults on rhDNase and adults ineligible, intolerant or inadequately responsive to rhDNase).

  Overall, eight RCT's with hypertonic saline were identified. As summarised in Appendix 5 of the submission, the hypertonic saline formulation differed across studies (3% to 7%) due to no standard therapeutic dose having been established. In addition, substantial differences were also observed in terms of inclusion/exclusion criteria and baseline study characteristics between trials. Thus, an indirect comparison between mannitol and hypertonic saline was not attempted in the pooled adult population or in any rhDNase adult subgroup.

- Why the economic model is not separately focussed on these two populations/comparisons[2]?

  See answer to first two bullet points. As already discussed, at the time of submission of this dossier, the rhDNase unsuitable population was considered too small for reliable analysis of effect of mannitol in the key efficacy endpoints. Nonetheless, this analysis has now been conducted and it shows that the beneficial effect of mannitol in terms of change in FEV_1 and PDPE incidence and rate is comparable between rhDNase users and rhDNase non-users or adults ineligible, intolerant or inadequately responsive to rhDNase. The only difference observed between the rhDNase users and non-users related to the CF treatment costs (excluding primary medication). However as the cost between the two arms remained small, it was decided not to distinguish between these subgroups in the model.

- Please could you run the economic model for these two populations separately (mannitol plus rhDNase versus rhDNase plus BSC in all adult CF patients; and mannitol alone versus BSC for CF patients who are ineligible, intolerant or

[2] Since initial manufacturer submission, the CHMP has granted Bronchitol the following license: "Bronchitol is indicated for the treatment of cystic fibrosis in adults aged 18 years and above as an add-on therapy to best standard of care". Current indication does not distinguish between adults on rhDNase and adults ineligible, intolerant or inadequately responsive to rhDNase.

inadequately responsive to rhDNase) and please provide all the necessary data for the ERG to replicate the economic model in these two populations?

In order to run the model for these populations, the effect on lung function was addressed in each population. Table 3 shows the parameter estimates of the final factors from the linear regression model. The details of each model can be found in Appendix A.

Table 3. Linear regression model results for FEV_1 % predicted at week 26

Variable	All adults (N=341)	rhDNase user (N=207)	rhDNase non-user (N=134)	rhDNase non-user unsuitable (N=65)
Intercept	-7.97	0.38	-4.23	-9.61
Mannitol	1.81	2.54	0.19	4.08
FEV_1 % predicted at baseline	0.93	0.94	0.91	0.83
Responder	5.23	4.55	6.07	5.43
BMI at baseline	0.38	NS	0.44	0.70
Improvement in resp symptoms	1.73	NS	NS	NS
Sa infection	NS	NS	-2.70	NS
Number of PDPEs	NS	NS	-2.83	NS

NS: Not statistically significant.

The calculated relative risk (RR) of experiencing a pulmonary exacerbation for mannitol responders is presented in Table 4. A Poisson regression analysis on the rate ratio for PDPE in the overall patient population (corrected for baseline rate and thus not taking into account the differences between historical pulmonary exacerbation rates observed in DMP-CF-302) showed that rhDNase is not a significant factor for the PDPE rate (see Appendix B); there was not sufficient data to run this analysis on the adult population. Due to the low patient numbers in each population there is high uncertainty around the RR in the specific populations. Therefore the analyses have been run on two scenarios: 1) assuming the relative risk in the 2 subpopulations was the same as for the overall adult population (0.65) and 2) taking the RR as calculated in each subpopulation.

Table 4. Relative risk of pulmonary exacerbation

Patient population		Control			Mannitol			RR
		N	# PDPE	PDPE rate	N	# PDPE	PDPE rate	
All adult	Non-responder	88	30	0.79	107	31	0.79	
	Responder	46	15	0.68	100	22	0.49	0.65
rhDNase user	Non-responder	57	18	0.75	69	20	0.80	
	Responder	28	10	0.75	53	16	0.68	0.91
rhDNase non-user	Non-responder	31	12	0.85	38	11	0.77	
	Responder	18	5	0.57	47	6	0.28	0.37
rhDNase non-user unsuitable	Non-responder	12	4	0.76	16	3	0.42	
	Responder	8	3	0.76	29	5	0.36	0.47

The probability of being a responder was analysed for each subgroup (see Table 5), as were the transition probabilities on improvement in respiratory symptoms (see Table 6 and Table 7).

Table 5. Responder rates

	All adults		rhDNase user		rhDNase non-user		rhDNase non-user unsuitable	
	n	%	n	%	n	%	n	%
Mannitol	100	48	53	43	47	55	29	64
Control	46	34	28	33	18	37	8	40

Table 6. Transition probabilities improvement in respiratory symptoms – rhDNase users

Treatment	Respiratory Symptoms	% of patients	n	N
Mannitol	Improved after 3 months	33%	34	102
	Remain improved after 6 months	68%	23	34
	Improved after 6 months but not at 3 months	13%	9	68
Control	Improved after 3 months	41%	31	76
	Remain improved after 6 months	74%	23	31
	Improved after 6 months but not at 3 months	20%	9	45

Table 7. Transition probabilities improvement in respiratory symptoms – rhDNase non-users unsuitable

Treatment	Respiratory Symptoms	% of patients	n	N
Mannitol	*Improved after 3 months*	*40%*	*16*	*40*
	Remain improved after 6 months	*63%*	*10*	*16*
	Improved after 6 months but not at 3 months	*25%*	*6*	*24*
Control	*Improved after 3 months*	*50%*	*9*	*18*
	Remain improved after 6 months	*78%*	*7*	*9*
	Improved after 6 months but not at 3 months	*11%*	*1*	*9*

The utilities for the health states CF and "CF improved RS" for Mannitol and Control were not changed as rhDNase was not significant in predicting the HUI2 score.

Univariate analysis showed that rhDNase use was a significant factor in overall 6-month treatment costs (excluding primary CF medication), but suitability to rhDNase was not significant (see Appendix B for details). Hence the 6-month treatment cost for each arm for patients who did not experience a pulmonary exacerbation were split for rhDNase users and non-users (see Table 8) and it was assumed that the rhDNase non-user unsuitable population would have the same cost as all rhDNase non-users.

Table 8. Mean 6-month CF-treatment cost (£)

	All adults (N=341)	rhDNase user (N=207)	rhDNase non-user (N=134)
Mannitol	*4,391*	*5,703*	*2,678*
Control	*4,664*	*5,389*	*3,279*
Total	*4,493*	*5,574*	*2,871*

The analyses were run on the same patient population parameters as those applied for the overall adult patient population (see Table 59 in submission).

Table 9. Results rhDNase user

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) versus baseline (QALYs)
RR exacerbation based on total adult population							
Control + rhDNase	261,529	11.23	9.62				
Mannitol + rhDNase	305,008	11.99	10.42	43,479	0.76	0.80	54,329
RR exacerbation based on rhDNase users adult population							
Control + rhDNase	261,529	11.23	9.62				
Mannitol + rhDNase	310,013	11.84	10.27	48,484	0.62	0.65	74,140
ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years							

Table 10. Results rhDNase non-user unsuitable

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) versus baseline (QALYs)
RR exacerbation based on total adult population							
Control	145,255	11.15	9.53				
Mannitol	184,944	12.50	10.96	39,689	1.35	1.43	27,673
RR exacerbation based on unsuitable adult population							
Control	145,255	11.15	9.53				
Mannitol	177,161	12.68	11.14	31,906	1.53	1.61	19,828
ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years							

A5. There seem to be a number of inconsistent assumptions in the MS:

- On page 14, it is assumed that low dose mannitol has no adverse events ("the safety profile of Mannitol, [mannitol 400 mg] BD can be assessed in the adult population as compared with the control group [50 mg mannitol]")

- On page 26, it is assumed that low dose mannitol can be considered similar in effectiveness to BSC ("Best supportive care will reflect the control arm from the two phase III studies")

- On page 81, it is assumed that low dose mannitol may show some degree of clinical activity ("The low dose formulation of Mannitol (control as used in DPM-CF-301 and DPM-CF-302) may show some degree of clinical activity which would preclude its use

as a common link to the hypertonic saline RCTs (control reported to be 0.9% saline [isotonic saline] as in 7/8 studies)").

Please provide an explanation for these apparent inconsistencies and, preferably, provide some evidence to support the assumptions.

- On page 14, it is assumed that low dose mannitol has no adverse events ("the safety profile of Mannitol, [mannitol 400 mg] BD can be assessed in the adult population as compared with the control group [50 mg mannitol]")

  The choice of low dose mannitol as control in the DPM-CF-301 phase III study was discussed with the CHMP/COMP who provided protocol assistance for this study (c.f., zipped folder "Protocol Assistance"). Both committees agreed that mannitol 40-50 mg would be an acceptable control in the trial to assess safety provided that the low dose of mannitol was not seen to be efficacious. Although the results of the DPM-CF-301 and 302 studies suggest some variable efficacy in children and adolescents, the mannitol 50 mg control was clearly shown to be sub-therapeutic in the adult population.

  As a result, data from DPM-CF-301 and DPM-CF-302 studies suggest that low dose mannitol may have had some beneficial effect on FEV_1 in the overall population, but this effect was not observed in the adult population. Any minor improvements, particularly in the first six weeks of the treatment period (see Table 26 of submission dossier) can be attributed to the patients' participation in a clinical trial resulting in better care and better compliance with background therapies rather than any significant contribution from the mannitol 50 mg in lung improvement. In the pivotal studies, and as observed in Table 26 of the submission dossier, the average change in FEV_1 from baseline for the low dose mannitol group in the DPM-CF-301 study ranged between +36.7 mL (SD: 185.25) at Week 6 and -29.0 mL (SD: 254.32) at Week 26, and between +41.4 mL (SD: 221.67) at week 6 and -64.7 mL (SD: 364.43) at week 26 in the DPM-CF-302 study. These changes suggest no effect of mannitol 50 mg. The changes in FEV_1 with mannitol 400 mg ranged between 100.3 – 133.8 mL and 57.5 – 116.1 mL in the DPM-CF-301 and DPM-CF-302 studies, respectively.

  Given the negligible efficacy effect of low dose mannitol in adults, it is reasonable to state that the safety profile of Bronchitol (mannitol 400 mg) b.i.d. can be assessed in

the adult population as compared with the control group (50 mg mannitol). Overall, the type and frequency of (serious) adverse events in the mannitol clinical studies are consistent with the underlying disease and its severity in CF patients. The majority of SAEs in the mannitol studies were considered unrelated to treatment and were consistent with the patients' relevant medical history and disease status.

Additional safety data from the long-term administration of mannitol in the open label phase of DPM-CF-301 (OLP and OLEP) and DPM-CF-302 (OLP) studies for both the overall population and the adult subpopulation are generally consistent with the safety data for the double-blind treatment phase of these studies.

- On page 26, it is assumed that low dose mannitol can be considered similar in effectiveness to BSC ("Best supportive care will reflect the control arm from the two phase III studies")

  The statement "best supportive care will reflect the control arm from the two phase III studies" implies that the control arm in both studies was the equivalent of best standard of care on the grounds that mannitol 50 mg should not have any effect in these patients.

  As already discussed above, low dose of mannitol does not have any beneficial effect in adults with CF. Data from the mannitol studies also highlight that low dose mannitol does not have any detrimental effect in these patients. Thus, addition of mannitol 50 mg to the best standard of care will not modify the effectiveness of the best standard of care in these patients.

- On page 81, it is assumed that low dose mannitol may show some degree of clinical activity ("The low dose formulation of Mannitol (control as used in DPM-CF-301 and DPM-CF-302) may show some degree of clinical activity which would preclude its use as a common link to the hypertonic saline RCTs (control reported to be 0.9% saline [isotonic saline] as in 7/8 studies)").

  Pharmaxis agrees that the argument above was not correctly formulated. Indeed, while low dose of mannitol (40 – 50 mg) may have some degree of clinical activity in children, it has been shown to be sub-therapeutic in adults in the dose-response study (DPM-CF-202) and in both phase III studies.

  Nevertheless, the main argument for not comparing mannitol to hypertonic saline was not the absence of a common control arm, but rather to significant differences in the

design and target population between the mannitol and the hypertonic saline studies. Of the eight RCT with hypertonic saline, only three were conducted solely in adults [Robinson 1996[3], 1997[4], 1999[5]]. The sample size of these three studies was very small (n = 10 – 12) and the treatment period duration was only one day in each study. Two additional studies were published only as abstracts [Button 1996[6]; Chadwick 1997[7]] and the treatment period was also significantly shorter than in the mannitol studies. The studies of Eng [Eng 1996[8]] and of Riedler [Riedler 1996[9]] had also a short treatment duration and in the latter study all patients (n = 10) were adolescents.

The only study that may have been pertinent for indirect comparison was the trial of Elkins et al (c.f., reference 29 of submission dossier). This study included children, adolescents and adults, but only data for the overall population was available. Importantly, this population did not appear to be optimally treated, based on current standard of care. Comparison between the overall population of the Elkins study and the adults from the mannitol studies was not deemed appropriate. Indirect comparison of the overall population from these studies was not feasible either, due to the low beneficial effect of low dose mannitol in children. Furthermore, as shown in the table below, baseline characteristics also differed between studies, particularly in terms of baseline FEV_1 predicted values, proportion of patients with pseudomona aeruginosa infection and antibiotic use. The FEV_1 was higher in the hypertonic saline study and the antibiotic use considerably lower than that reported in the Mannitol studies and current standard care. As presented in Table 11, the effect of hypertonic saline on the rate of PDPE was more pronounced than that of Mannitol (although reduction in incidence was comparable in DPM-CF-301). A direct comparison is not meaningful however in light of the considerably higher proportion of patients on antibiotics in the mannitol studies. The heavy antibiotic medication load in these patients inevitably set a higher hurdle above which additional benefit had to be

[3] *Robinson M, Regnis J, Bailey DL, King M, Bautovich G, Bye PTP. The effects of hypertonic saline, amiloride and cough on mucociliary clearance in patients with cystic fibrosis. American Journal of Respiratory and Critical Care Medicine 1996;153:1503-9.*
[4] *Robinson M, Hemming A, Regnis J,Wong A, Bailey D, Bautotvich G, et al. Effect of increasing doses of hypertonic saline on mucociliary clearance inpatients with cystic fibrosis. Thorax 1997;52(10):900-3.*
[5] *Robinson M, Daviskas E, Eberl S, Baker J, Chan H, Anderson, S, et al. The effect of inhaled mannitol on bronchial mucus clearance in cystic fibrosis patients: a pilot study. European Respiratory Journal 1999;14:678-85.*
[6] *Button BM, Riedler J, Eng P,RobertsonCF. Inhaled hypertonic saline as an adjunct to chest physiotherapy in cystic fibrosis; the three year clinical experience [abstract]. Pediatric Pulmonology 1996;Suppl 13: 306.*
[7] *Chadwick SL, Moss SJ, Bott J, Geddes DM, Alton EWFW. Effect of hypertonic , isotonic saline and water challenges on the airways of cystic fibrosis patients [abstract]. Thorax 1997;52(Suppl 6):A43.*
[8] *Eng PA, Morton J, Douglass JA, Riedler J, Wilson J, Robertson CF. Short-term efficacy of ultrasonically nebulized hypertonic saline in cystic fibrosis. Pediatr Pulmonol. 1996 Feb;21(2):77-83.*
[9] *Riedler J, Reade T, Button B, Robertson CF. Inhaled hypertonic saline increases sputum expectoration in cystic fibrosis. J Paediatr Child Health. 1996 Feb;32(1):48-50.*

demonstrated. Despite the low antibiotic use in the Elkins study (approximately 50% of patients), the proportion of patients with pseudomona aeruginosa in suptum at baseline was substantial (78% and 79% of patients in the control and hypertonic saline, respectively). In contrast, mannitol had a higher effect on change of FEV_1 than hypertonic saline despite the higher concomitant medication.

Table 11. Comparison between the Elkins and the Mannitol studies

	Elkins 2006		DPM-CF-301 (adults)		DPM-CF-302 (adults)	
	HS*[4]	Control	Mannitol	Control	Mannitol	Control
Age (yrs)*[1]	18.4±9.3	18.7±9.2	29.6±9.42	28.8±8.49	24 (18;48)	27 (18;53)
Regular use of antibiotics, n (%)	40 (49.4)	42 (50.6)	167 (94.4)*[3]	105 (89.0)*[3]	140 (76.1)*[3]	97 (80.2)*[3]
Pseudomonas aeruginosa in sputum, n (%)	45 (78)	49 (79)	76 (67)	51 (67)	43 (46)	33 (57)
Baseline FEV_1 (mL)	85.0±18.0	88.0±18.0	58.1±15.91	57.3±16.79	61.9±15.0	59.8±14.3
FEV_1 change from baseline difference*[2]	68.0 [3.0 – 132.0]		105.5 [40.3 – 170.8]		118.5 [10.4 – 226.7]	
PDPE per pat/year	0.39	0.89	1.05	1.43	0.46	0.29

**1 All data are provided as mean (±SD) except for study DPM-CF-302 where data correspond to median (range).*
**2 Mean change is from week 26 in the mannitol studies and from week 48 in the Elkins study. Values correspond to mean and ranges.*
**3 These values correspond to the overall ITT population (including children and adolescents).*
**4 HS: hypertonic saline.*

The above arguments precluded an indirect comparison between mannitol and hypertonic saline.

A6. The ERG note that the current report does not assess the cost-effectiveness of mannitol compared with hypertonic saline as outlined in the scope. Please could you consider providing additional economic analysis of mannitol as a replacement for hypertonic saline (Chapter 6.2)?

See answer to question A5. Due to significant differences in the design and population between the mannitol and the hypertonic saline studies it is not feasible to compare mannitol to hypertonic saline. Moreover, in clinical practice, mannitol will not replace hypertonic saline when hypertonic saline is seen to be effective and well tolerated in an individual. The perceived role of hypertonic saline would appear to be different to that of rhDNase or mannitol as hypertonic saline is being used as an aid to physiotherapy.

Pharmaxis were part of a cohort of sponsors of an independently created quantitative market research monitor (CF Monitor) that was conducted in the latter half of 2010 by Synovate Healthcare. This involved feedback from 100 CF physicians across 5 European

countries, including 20 CF physicians from across the UK, and consideration of more than 1,000 CF patient histories (200 patients in the UK).

Only 6% of CF patients considered were taking hypertonic saline as a sole lung clearance agent, compared with 42% who were taking rhDNase (a figure similar to that identified in the latest published report of the CF Trust UK Registry). The low use of hypertonic saline among patients with cystic fibrosis also highlights that it would be an inappropriate comparator to mannitol.

Treatment with rhDNase was primarily initiated because of severity of lung disease and rate of lung function decline, whereas the primary reason for initiation of hypertonic saline was to aid physiotherapy (64%). In line with this, an expert panel were interviewed following an introduction to the clinical data of mannitol. They stated that mannitol was most likely to be prescribed to patients with more severe lung disease – i.e.: a similar patient group to those were utilising rhDNase [data on file].

A7. Please explain why the probability to switch to control in the model is only based on the response rate found in the trial, not including the withdrawal rate. Please could you conduct an additional analysis including withdrawal rate for switching to control treatment. (Chapter 6.3)

Patients (adults) withdrawing from the study have been partially included in the probability to switch to control. All drop-outs (i.e., patients with missing values for FEV_1 at the 6-week visit) have been considered to be non-responders and switched to control. Only patients withdrawing after the initial 6 weeks were assumed to remain in the model. The rationale for not building treatment switch for responders was that the majority of drop-outs occurred in non-responders and within the first 6 weeks of the study (see Table 12), and that withdrawal after the initial 6 weeks was comparable between both treatment arms. It was felt that including switching for responders would unnecessarily complicate the model.

A sensitivity analysis including drop-out due to withdrawal is shown in Table 14. Twenty-six patients in the mannitol arm withdrew from the study between visit 2 and the end of the double-blind phase. Of those 26 patients, 15 patients responded to treatment after the initial 6 weeks corresponding to 8.0% of patients after 14 weeks and another 7.6% after 26 weeks. It was assumed that all patients who completed the 26-week treatment period would continue with mannitol treatment until they died or received a lung transplant.

Table 12. **Number of withdrawals by study and by visit**

Visit	Population	Control			Mannitol		
		DPM-CF-301	DPM-CF-302	Total	DPM-CF-301	DPM-CF-302	Total
Baseline	Responder	0	0	0	0	0	0
	Non-responder	0	0	0	2	0	2
	Total	0	0	0	2	0	2
Week 6	Responder	0	1	1	5	3	8
	Non-responder	7	2	9	18	12	30
	Total	7	3	10	23	15	38
Week 14	Responder	2	0	2	7	1	8
	Non-responder	7	1	8	7	3	10
	Total	9	1	10	14	4	18
Week 26	Responder	5	2	7	3	4	7
	Non-responder	3	2	5	1	0	1
	Total	8	4	12	4	4	8
Overall	Responder	7	3	10	15	8	23
	Non-responder	17	5	22	28	15	43
	Total	**24**	**8**	**32**	**43**	**23**	**66**

Table 13. Probability of Mannitol responders switching due to treatment withdrawal

Visit	n	N	pSwitch
Week 14	8	100	8.0%
Week 26	7	92	7.6%

Table 14. Result sensitivity analysis switching due to withdrawal

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) versus baseline (QALYs)
Control	180,188	11.40	9.75				
Mannitol	208,024	12.05	10.46	27,835	0.65	0.71	39,473
Control + rhDNase	249,472	11.40	9.75				
Mannitol + rhDNase	281,625	12.05	10.46	32,153	0.65	0.71	45,596
ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years							

A8. Please could you provide data (per trial and the trials combined) regarding unacceptability of mannitol to patients, drop-out rate, non compliance due to side effects both for mono-therapies and combination treatments?

Acceptability of mannitol by patients was not specifically addressed in the study. However, treatment burden was assessed with the Burden of Treatment domain of the CFQ-R. This

domain is scored based on 3 questions: the extent that treatments make daily life more difficult, the time spent each day on treatments, and difficulty preparing treatments (including medications) each day. The pooled data showed no difference between groups, providing assurance that Bronchitol was well tolerated in the majority of patients, and there was no meaningful treatment burden in either treatment group as a result of administering 10 capsules b.i.d.

The withdrawal rate was higher in the DPM-CF-301 study (Table 15). The higher rate was mainly driven by a higher proportion of patients withdrawing during the first six weeks of treatment (the most common adverse event leading to withdrawal was cough, and most of these patients withdrew on day of first visit); no differences were observed between the DPM-CF-301 and DPM-CF-302 studies after week 6. Lower early withdrawal rate in the DPM-CF-302 study is likely due to the additional training on the inhaler technique and the information provided to patients regarding coughing in this study. Thus, the withdrawal rate observed in study DPM-CF-302 is likely to represent better what may happen in a real clinical setting. The withdrawal rate for the pooled adult patient population treated with mannitol was 34.4% for the rhDNase users and 28.2% for the non rhDNase users.

While treatment compliance at each visit was recorded in the studies' CRF, non compliance due to side effects was not specifically addressed in these studies. Treatment compliance was determined by counting returned unused medication and empty blister packaging. Compliance was considered acceptable at ≥60%, based on levels of compliance levels observed in other CF studies. Compliance over 26 weeks was estimated to exceed 60% in 83.6% of ITT population (children, adolescents and adults) and was consistent throughout the study period in DPM-CF-301. In fact, the average compliance was 89% in DPM-CF-301 and 94% in DPM-CF-302 (ITT population). This suggests that 10 capsules per dose is acceptable to most patients and that there should be no major concern regarding compliance following anticipated approval. Direct tolerability questions support this.

Although non-compliance specifically due to side effects was not collected in the Bronchitol studies, compliance rate in adults who experienced at least one adverse event during the double-blind treatment period did not differ from compliance of the overall population (Table 15). Compliance rate in adults withdrawn prematurely due to AEs during the double blind phase of the study was also similar to compliance in the overall adult population (Table 15).

Table 15. Withdrawal and compliance rate for adults in the pivotal phase III studies

	DPM-CF-301				DPM-CF-302				Pooled population			
	Mannitol (n=114)		Control (n=76)		Mannitol (n=93)		Control (n=58)		Mannitol		Control	
	Users (n=58)	Non users (n=56)	Users (n=44)	Non users (n=32)	Users (n=64)	Non uses (n=29)	Users (n=41)	Non users (n=17)	Users (n=122)	Non users (n=85)	Users (n=85)	Non users (n=49)
Withdrawal rate, % (n)	41.4 (24)	33.9 (19)	36.4 (16)	25.0 (8)	28.1 (18)	17.2 (5)	14.6 (6)	11.8 (2)	34.4 (33)	28.2 (29)	25.9 (13)	20.4 (5)
Compliance in patients withdrawn due to AEs, % compliance (n)												
Based on last day of FU*[1]	42.5 (14)	67.9 (9)	62.3 (7)	54.4 (7)	45.0 (8)	16.7 (1)	52.7 (2)	n=0	44.5 (22)	62.8 (10)	60.1 (9)	54.4 (3)
Based on last day reported by patient*[2]	65.3 (14)	106.9 (9)	89.5 (3)	70.1 (3)	71.4 (8)	87.5 (1)	74.3 (2)	n=0	84.5 (22)	104.9 (10)	86.1 (9)	70.1 (3)
Compliance in patients with AEs, % compliance (n)												
Based on last day of FU	26 (60.5)	22 (74.3)	19 (65.5)	13 (86.5)	56 (80.4)	27 (86.7)	34 (88.2)	15 (90.5)	82 (74.1)	49 (79.6)	53 (80.0)	28 (88.7)
Based on last day reported by patient	26*[3] (500.7)	22 (93.6)	19 (81.5)	13 (97.2)	56 (89.6)	27 (89.5)	34 (91.5)	15 (93.3)	82*[3] (219.9)	49 (89.5)	53 (87.9)	28 (95.1)

*[1] This corresponds to compliance taking the last day of follow up (FU) as the last day on treatment.
*[2] This corresponds to compliance taking the last day of treatment reported by the patient as the last day on treatment.
*[3] Compliance for two of the adults was 5600%.

A9. The ERG note that the analyses in appendix 15 indicate that treatment is not a significant covariate in predicting HUI2 utility score. (Chapter 6.4 and 6.5). Please could you clarify why costs and utilities in the model are treatment dependent?

Multivariate analysis showed that baseline utility score and improvement in respiratory symptoms were the only significant covariate in predicting HUI2 utility score, although the model was weak (adjusted R-square of 0.17).

It was decided to keep these cost and utility parameters treatment dependent as all other input parameters were treatment independent. We acknowledge that this is a major assumption, hence sensitivity analyses were performed with equal cost and utility (see Table 127 in section 9.18).

Univariate analysis on the overall pooled population showed that pulmonary exacerbations, lung function, and rhDNase use were the most significant factors in predicting total 6-month treatment cost (excluding CF medication cost). In patients who did not experience a pulmonary exacerbation, the univariate analysis showed that rhDnase use and lung function remained significant (see Appendix C). There was not enough information available to split cost by lung function strata. Treatment cost could have been separated for rhDNase user versus non-user (see Table 8), but as all clinical input parameters (effect on lung functioning, pulmonary exacerbations, etc) were based on the overall patient population and rhDNase use was non-significant in any of these analyses, it was decided not to separate the costs. A sensitivity analysis where the 6-month CF treatment costs were split by rhDNase use and treatment group is presented in Table 16.

Table 16. Result sensitivity analysis CF treatment cost split by rhDNase user/non-user

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) versus baseline (QALYs)
Control	149,019	11.40	9.75				
Mannitol	174,578	12.10	10.52	25,558	0.70	0.77	33,080
Control + rhDNase	265,776	11.40	9.75				
Mannitol + rhDNase	310,591	12.10	10.52	44,815	0.70	0.77	58,004
ICER, incremental cost-effectiveness ratio; incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years							

A10. Please explain why probability of hospitalisation due to exacerbation is treatment independent, but length of stay in a hospital is treatment dependent (Chapter 6.4 and 6.5)?

Only the probability of experiencing a pulmonary exacerbation was assumed treatment dependent (see section 6.3.1 Table 56). The cost of treating a pulmonary exacerbation was assumed to be treatment independent as there were not enough patients to differentiate between treatment group (see section 6.5.3 Table 83). The length of the detrimental effect of a pulmonary exacerbation was also assumed to be treatment independent (see section 6.4.9). This value was based on the median duration of an IV antibiotic treatment course (14 days) as reported in the UK CF registry report[10]. The value was not taken from the pooled hospitalisation data as it was not consistently reported whether the hospitalisation was due to a pulmonary exacerbation (this was available for only 34 out of 76 patients). However, when looking at the average length of stay for admissions due to pulmonary exacerbations, the average length of stay was comparable between both treatment groups (see Table 17), thus the assumption that the duration of the detrimental effect of a pulmonary exacerbation is equal in both treatment groups seems reasonable.

Table 17. Length of stay for admissions for pulmonary exacerbations.

Statistic	Control	Mannitol	Total
N	10	24	34
Average	11	11	11
StdDev	6	7	7
Min	1	1	1
Max	18	29	29

A11. Please could you provide a sensitivity analysis with treatment independent costs and utilities (Chapter 6.4 and 6.5)?

This sensitivity analysis is presented in Table 127 in section 9.18 (Appendix 18: Additional scenario analyses) in the submission.

The cost and utility values that were used in this analysis were treatment independent and are presented in Table 18.

[10] *UK CF Registry. Annual Data Report 2008.*
*http://www.cftrust.org.uk/aboutcf/publications/cfregistryreports/UK_CF_Registry-*Annual_Data_Report_2008.pdf

Table 18. Utility and cost input parameters used in sensitivity analysis assuming treatment independent costs and utilities

Variable name	*Description*	*Value*
d_u_improvRS_B	*Change in utility from baseline for patients treated with mannitol with improvement in respiratory symptoms*	*0.015*
d_u_improvRS_C	*Change in utility from baseline for patients treated with supportive care (control) with improvement in respiratory symptoms*	*0.015*
d_u_no_improvRS_B	*Change in utility from baseline for patients treated with mannitol without improvement in respiratory symptoms*	*-0.031*
d_u_no_improvRS_C	*Change in utility from baseline for patients treated with supportive care (control) without improvement in respiratory symptoms*	*-0.031*
c_CF_B	*Total 6-monthly cost per CF patient treated with mannitol*	*4,493*
c_CF_C	*Total 6-monthly cost per CF patient treated with control*	*4,493*

A12. In the model there is an implicit assumption that best supportive care is equal to best supportive care + rhDNase in terms of effectiveness. Please could you provide details of any evidence for this assumption; the ERG note that there is a Cochrane review showing effects of rhDNase (Wark et al. CD001506)?

The submission does not intend to imply that best supportive care is equal to best supportive care plus rhDNase. The assumption made is that the effectiveness of mannitol is independent of the use of rhDNase. This is supported by the fact that rhDNase was not significant in predicting a patient's lung function (see section 9.14).

The ERG is correct that the comparison of Mannitol to Control + rhDNase cannot be made and that the results presented in Table 94 may be misleading. The incremental results reported for the Control + rhDNase should be ignored, as the submission intends to make the following 2 comparisons only (see Table 19*):*

1. *Mannitol versus Control*
2. *Mannitol + rhDNase versus Control + rhDNase*

Table 19. Base case result (update of Table 94 of submission)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incr (QALYs)
Control	180,188	11.40	9.75					
Mannitol	211,923	12.10	10.52	31,735	0.70	0.77	41,074	41,074
Control + rhDNase	249,472	11.40	9.75	~~69,284~~	~~0.00~~	~~0.00~~	~~dominated~~	~~dominated~~
Mannitol + rhDNase	285,858	12.10	10.52	36,386	0.70	0.77	~~136,768~~	47,095
ICER, incremental cost-effectiveness ratio; incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years								

Section B - Clarification on clinical and cost effectiveness

B1. Please could you clarify how many patients in trials 301 and 302 did not pass the mannitol tolerance test (MTT)? Please could you also clarify which adverse events were reported during the screening period?

The proportion of adults not eligible for mannitol treatment per mannitol trial and for the pooled population is provided in the table below. The overall proportion of adults not suitable (i.e., with a positive mannitol challenge or who failed to complete the test) was 9.6%.

Table 20. Mannitol tolerance test results for adults in the DPM-CF-301 and DPM-CF-302 studies

	DPM-CF-301		DPM-CF-302		Pooled population	
	N	%	N	%	N	%
Entered (enrolled in study)	245	100%	170	100%	415	100%
Positive Mannitol challenge	19	7.8%	8	4.7%	27	6.5%
Failed to complete mannitol test	9	3.7%	4	2.4%	13	3.1%
Total	28	11.4%	12	7.1%	40	9.6%

Overall, 10.3% (75/729) of all patients screened (children, adolescents and adults) had at least one adverse event between the time of MTT and the day after, and 20.4% (149/729) between day 2 of MTT and day of study medication initiation. The most commonly reported adverse event during the first 24 hours after MTT was cough (n=26; 3.6%). All other adverse events were reported by less than 1% of patients.

The most commonly reported adverse events between day 2 of MTT and study medication initiation were condition aggravation (n=55; 7.5%), upper respiratory infection (n=9; 1.2%) and cough (n=9; 1.2%). All other adverse events were reported by less than 1% of patients.

B2. Please explain the rationale for the health state definitions in the economic model. The ERG note that the relative definition of the health states 'CF' and 'improved CF' implies a very heterogeneous patient population in each health state (with respect to FEV1, and exacerbation rate; utility and costs can be expected to differ due to variation in absolute FEV1).

As specified in the final scope, the key outcomes to be considered included mortality, lung function, respiratory symptoms, reduction in pulmonary exacerbations, exercise tolerance and health-related quality of life. As described in section 6.2.5 of the submission, improvement in respiratory symptoms as measured by the CFQ-R was a significant factor in predicting a patient's QoL. Neither excercise tolerance nor vitality proofed to be significant. Thus based on the effect on a patient's QoL two separate health states were constructed to capture the impact of improvement in respiratory symptoms. It is recognised that the effect of improvement in respiratory symptoms is small, hence a sensitivity analysis was performed on the impact of improvement in respiratory symptoms (see Table 125, section 9.18).

B3. Please explain the role of categorising FEV1-predicted in the model (>80; 60-79; 40-59; <40) in relation to age and BMI.

In the subgroup analysis presented in section 6.9.4 (Table 103) the patient characteristics were determined for each lung function group as the patient characteristics differed by group. Age increased and BMI decreased with worse lung functioning (see Table 21).

Table 21. Mean age and BMI by lung function

Parameter	ppFEV≥80	ppFEV 60-79	ppFEV 40-59	ppFEV<40	All adults
N	33	131	138	39	341
Mean age (years)	24.39	28.00	29.47	30.38	28.52
Mean BMI (kg/m²)	22.94	22.76	22.30	21.04	22.39

B4. Table 67. Please explain why no interaction terms were included in the BioGrid analysis of survival (Adults only). Please also clarify why the analysis excluded people aged over 47 years when there is a model that includes all ages? (Chapter 6.3.7)

A model that contained interactions between gender and the other main predictors (ppFEV1, BMI, hosp_days/qtr>0 and before 2000) showed that none of these interaction terms were significant.

Initially all ages in the data (6 to 69) were used. However, later it was considered more appropriate to use a subset of the data that pertained to adults (≥ 18 years) and ages where there were at least 20 observations/year, i.e. ≤ 47 years (see Table 6, BioGrid report, section 9.16 of the submission).

The models for all ages and years 18 to 47 are both shown for the purposes of comparison. Although the Chi-square for ppFEV$_1$ is not as large in the latter model it is still highly significant. However, BMI is not significant in the latter model probably because on average BMI is constant in adult patients.

B5. Please explain how the hazard ratio for FEV1 (Table 69) was used (transformed) for transition probability 'pDie' in the model. Please could you clarify which baseline function or baseline probability was used when applying the hazard ratio. (Chapter 6.3.7)

The probability to die in the model is calculated using the life table method (depending on the age and gender of the patient) corrected for the HR for FEV$_1$ % predicted based on the difference of a patient's FEV$_1$ % predicted at a certain time point from the overall mean FEV$_1$ % predicted observed in the BioGrid patient sample (see Table 4, BioGrid report, section 9.16 of the submission).

*For male patients the formula is: pDie = 1-Exp(-Mortality_CF[tAge;3]*HR_FEV^(tFEV-58.57)*_CycleLength)*

*For female patients the formulat is: pDie = 1-Exp(-Mortality_CF[tAge;4]*HR_FEV^(tFEV-61.48)*_CycleLength)*

B6. Please explain why BMI is included in the regression model if it is not included in the health economics model? If BMI is excluded because of non-significance, the Cox model should be rerun with only ppFEV1 as a covariate (6.3.7)

The COX model with only ppFEV1 for patients aged between 18 and 47 is presented in Table 22, Table 23 and Figure 3 below.

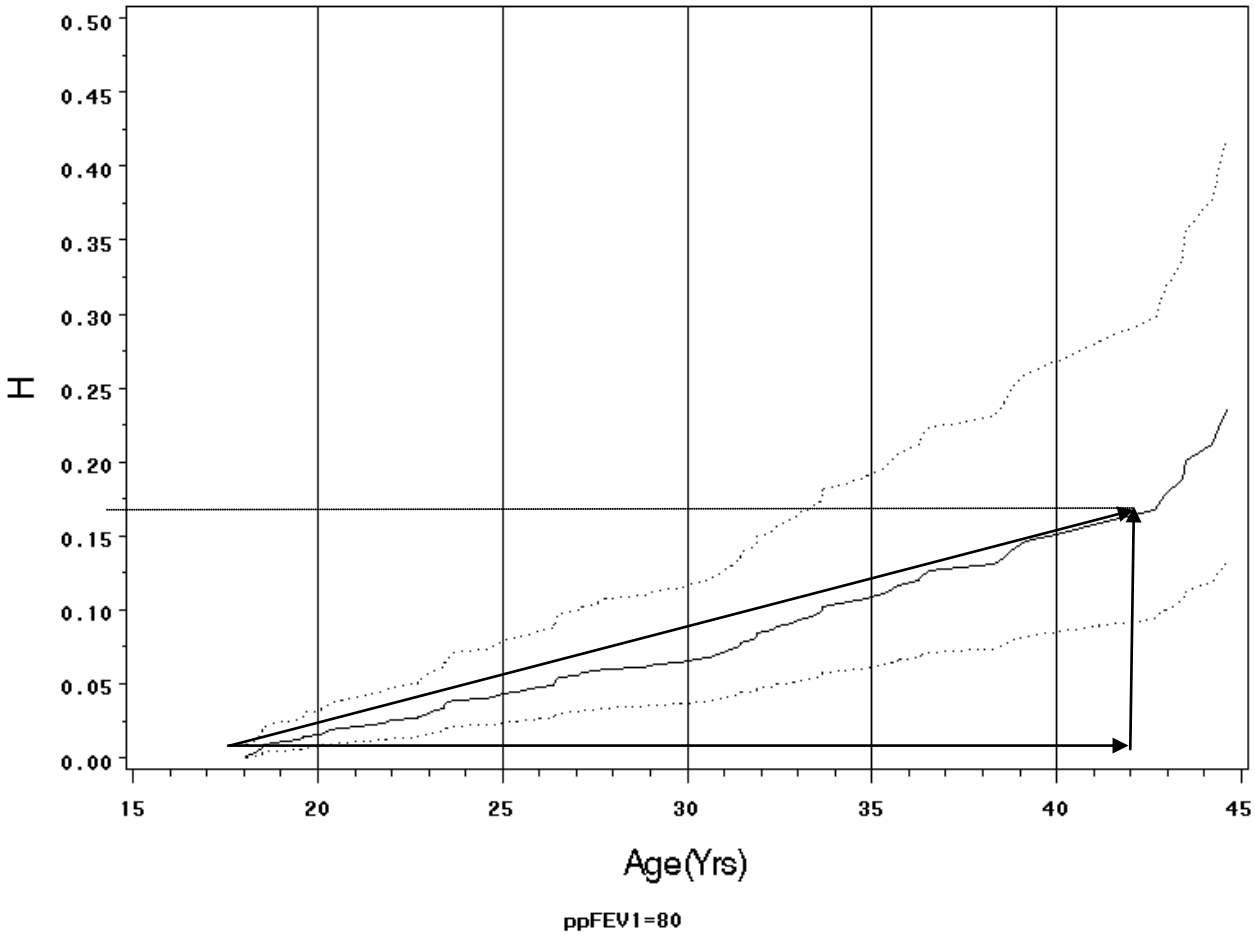
Table 22. Statistics for testing the model with the null hypothesis

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	68.5680	1	<.0001
Score	56.7981	1	<.0001
Wald	52.8923	1	<.0001

Table 23. Parameter estimates and significance using the maximum likelihood estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
ppFEV1	*1*	*-0.04879*	*0.00671*	*52.8923*	*<.0001*	*0.952*

Figure 3. Baseline cumulative hazard



The baseline cumulative hazard increases linearly from 0 to 0.16 from ages 18 to 42.5 to give a constant slope (hazard rate) ((0.16-0)/(42.5-18)) of 0.0065.

Rerunning the base case analysis with an HR of 0.952 instead of 0.957 gave very similar results, see Table 24.

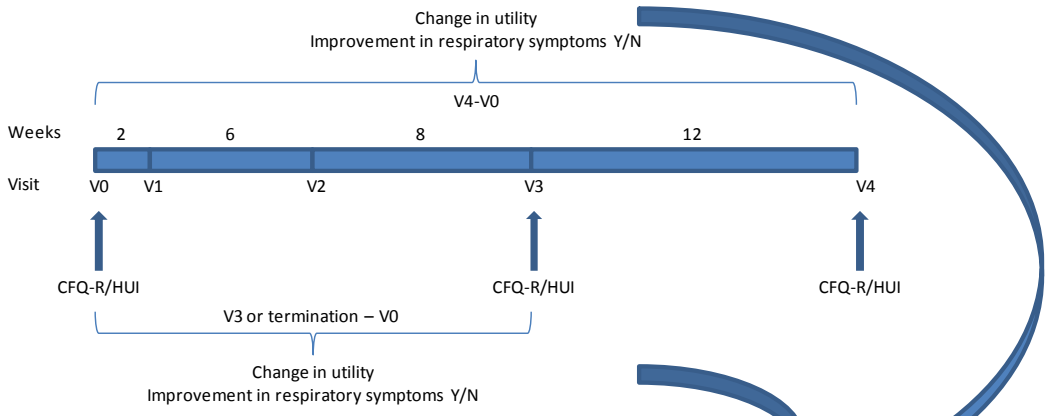
Table 24. Results sensitivity analysis with HR of 0.952

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) versus baseline (QALYs)
Control	*178,730*	*11.32*	*9.86*				
Mannitol	*211,794*	*12.09*	*10.61*	*33,064*	*0.77*	*0.75*	*44,073*
Control + rhDNase	*247,584*	*11.32*	*9.86*				
Mannitol + rhDNase	*285,728*	*12.09*	*10.61*	*38,144*	*0.77*	*0.75*	*50,845*
ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years							

B7. Please explain the reason why in bullet point 2 of the description of how the utility scores were estimated, the change from baseline is calculated separately for V3 and V4. It is not clear how this is used to fill table 74. (Chapter 6.4.9)

The two CF health states in the model are based on an improvement in respiratory symptoms which was defined as an improvement of at least 4 points from screening in the respiratory domain score of the CFQ-R. Both the CFQ-R and the HUI were administered at the 14-week and the 26-week visit (in the DPM-CF-302 study). For both visits it was determined whether the patient had improvement in respiratory symptoms or not and what the change in utility from screening was. Since the health states are based on an improvement in respiratory symptoms compared to the screening visit, we assumed no difference in utility between a patient having improvement after 14 or 26 weeks and averaged them to obtain the change in utility for both health states (see Figure 4).

Figure 4. Calculation of utility scores by health state



Average change in utility from baseline by treatment group and respiratory symptoms

	Control	Bronchitol
Improved	0.009	0.019
Not improved	-0.046	-0.022

B8. Table 74: please explain why only the paper by Anyanwu was used to estimate utility pre- and post-lung treatment when 3 relevant references were found. (Chapter 6.4.9)

The paper by Anyanwu[11] was used because it was the only UK study that was identified, had the greatest sample size and reported standard deviations.

The data from Groen[12] only reported the mean EQ-5D values which were higher than the values reported by Anyanwu[11], but did not report the diagnosis or type of lung transplant. The utilities in the Vasiliadis paper[13] were based on a very small sample size. The reported utility for patients on the LT waiting list was lower than measured by Anyanwu[11], but they reported that the time on waiting list was rather short (9 months). The reported utility values post lung transplant in CF/bronchiectasis patients corresponded well to the values reported by Anyanwu[11] (average post lung transplant 0.80 versus 0.77).

Finally, sensitivity analyses showed that the utility for patients on the lung transplant waiting list and post lung transplant had only a minor impact on the ICER.

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[11] *Anyanwu AC, McGuire A, Rogers CA, Murday AJ. "Assessment of quality of life in lung transplantation using a simple generic tool." Thorax. 2001;56(3):218-22.*
[12] *Groen, H., W. van der Bij, G. H. Koeter and E. M. TenVergert. "Cost-effectiveness of lung transplantation in relation to type of end-stage pulmonary disease." Am J Transplant 2004: 4(7): 1155-62*
[13] *Vasiliadis HM, Collet JP, Penrod JR, Ferraro P, Poirier C. "A cost-effectiveness and cost-utility study of lung transplantation" J Heart Lung Transplant. 2005;24(9):1275-83*

B9. Please explain how the utilities at the various time points post-treatment were combined to in one utility estimate of 0.8. (Chapter 6.4.9)

The utility post transplant was the average of the mean EQ-5D scores for patients who had a bilateral lung transplant as reported by Anyanwu[11] (see Table 25). As the reported utility score varied very little over time, the overall average was applied to the entire post lung transplant period.

Table 25. Mean utility scores after bilateral lung transplantation

Months after transplant	N	Mean EQ-5D
0-6 months	14	0.75
7-18 months	16	0.83
19-36 months	21	0.81
>36 months	28	0.82
Average after bilateral LT	**79**	**0.80**

B10. In Table 82, please provide a column for the total population (i.e. mannitol plus control). Additionally, please provide the numbers on which each mean total cost is based, and the standard errors of these means. (Chapter 6.5)

The total costs, the standard deviation and the number on which each mean total cost is based are presented in Table 26.

Table 26. Six-month CF treatment cost (update of Table 82 in submission)

	Cost (£)	Mannitol			Control			Total		
		N	Mean	SD	N	Mean	SD	N	Mean	SD
No PDPE in trial period	Medication	166	2,871	4,390	99	2,617	2,713	265	2,776	3,846
	Community visits	166	48	92	99	53	122	265	50	104
	Hospitalisations	166	1,471	4,323	99	1,994	4,474	265	1,666	4,379
	TOTAL	166	4,391	7,136	99	4,664	5,492	265	4,493	6,560
PDPE in trial period	Medication	41	4,797	3,919	35	3,976	4,047	76	4,419	3,973
	Community visits	41	62	93	35	53	99	76	58	95
	Hospitalisations	41	7,994	6,829	35	6,325	7,561	76	7,225	7,176
	TOTAL	41	12,852	7,959	35	10,354	10,445	76	11,702	9,210
All patients	Medication	207	3,253	4,360	134	2,972	3,157	341	3,142	3,929
	Community visits	207	51	92	134	53	116	341	52	102
	Hospitalisations	207	2,763	5,551	134	3,125	5,745	341	2,905	5,622
	TOTAL	207	6,067	8,032	134	6,150	7,510	341	6,100	7,820

B11. In Table 85, please explain why an exponential distribution was assumed for the cost of pulmonary exacerbation, cost of lung transplant and cost post-lung treatment. (Chapter 6.5)

The total mean 6-month treatment cost for patients experiencing 1 pulmonary exacerbation (N=55) during the blinded phase was £10,608 (interquartile range £4,869 to £13,505; min £107 to max £54,050) corresponding to an estimated cost to treat the pulmonary exacerbation of £6,115. The exponential distribution was chosen as this distribution seemed to best match the distribution of the data.

The cost of a lung transplant as reported by the NHS is £35,458 with an interquartile range of £11,054 to £63,995. This matched better with an exponential distribution (interquartile range £10,201 to £49,155) than a gamma distribution.

The post-transplant costs were derived from Anyanwu[14] who did not report the standard deviation or the distribution of the costs. In line with the observed range for lung transplant costs it was assumed an exponential distribution would apply. Sensitivity analysis showed that the impact of neither transplant nor post-transplant cost are significant in the model.

B12. Table 95 Results PSA – Monotherapy: Please provide 2 separate tables instead of table 95, one giving the results for the patient population for which mannitol is second line treatment and/or contraindicated and one giving the results for the patient population for which mannitol is add-on drug. (Chapter 6.7.6)

Table 27 and Table 28 below present the probabilistic sensitivity results for the two subgroup analyses performed as described in question A4 fourth bullet point. The distribution of the relative risk for the pulmonary exacerbation rate in mannitol responders was based on the overall pooled adult patient population.

Table 27. Results PSA – rhDNase users

Statistic	Cost intervention (Mannitol + rhDNase)	Cost comparator (Control + rhDNase)	Incr cost	QALY intervention (Mannitol + rhDNase)	QALY comparator (Control + rhDNase)	Incr QALY	ICER
Mean	305,261	261,509	43,752	9.66	8.79	0.87	53,796
Median	284,047	240,292	44,916	9.69	8.83	0.85	51,715
StDev	68,345	74,395	11,530	0.83	0.86	0.30	281,899
Min	218,565	173,330	-41,580	6.85	5.79	-0.23	-7,548,421
Max	757,057	775,782	84,594	12.10	11.94	1.98	4,271,375
2.5% percentile	233,988	185,765	18,399	7.97	7.06	0.26	14,553
97.5% percentile	482,411	465,971	62,567	11.26	10.43	1.48	132,662

[14] *Anyanwu AC, McGuire A, Rogers CA, Murday AJ. J "An economic evaluation of lung transplantation." Thorac Cardiovasc Surg. 2002;123(3):411-8; discussion 418-20.*

Table 28. Results PSA – rhDNase non-users unsuitable to rhDNase

Statistic	Cost intervention (Mannitol)	Cost comparator (Control)	Incr cost	QALY intervention (Mannitol)	QALY comparator (Control)	Incr QALY	ICER
Mean	185,480	145,698	39,782	10.28	8.77	1.51	30,080
Median	166,269	123,889	42,339	10.32	8.74	1.51	27,666
StDev	63,061	70,831	16,888	0.92	0.97	0.47	19,706
Min	104,624	61,315	-55,480	7.01	5.76	0.20	-35,753
Max	535,095	559,419	134,498	13.39	12.22	3.03	226,289
2.5% percentile	120,432	72,244	-3,784	8.46	6.85	0.56	-1,988
97.5% percentile	365,795	338,087	62,627	12.03	10.69	2.44	77,176

B13. Please clarify the mean ICER of £43,703 per QALY gained and its confidence intervals, how has this been obtained? Also please clarify to which population this ICER applies. (Chapter 6.7.8)

The ICER applies to the comparison of Mannitol to Control. The ICER of £43,703 refers to the PSA to the report submitted on the 11th of February (version 5), and was mistakenly not updated in the final submission (version 7). The correct figures are displayed in Table 97 of the submission: mean ICER £46,401 (95% CI -£1,547 to £118,008).

B14. Please clarify for figure 25 to which population each curve applies. (Chapter 6.7.8)

The blue curve corresponds to the comparison of Mannitol to Control; the red curve corresponds to the comparison of Mannitol + rhDNase to Control + rhDNase.

B15. Please provide scenario analysis on the percentage of compliance / adherence to treatment. (Chapter 6.7.9)

Rather than assuming that the patients' drug utilisation was as specified by the protocol, it would have been possible to use the data on compliance to adjust the CF medication costs. The overall compliance based on last date of treatment in the double blind phase from the pooled adult data from DPM-CF-301 and DPM-CF-302 is presented in Table 29. The results suggest that compliance rates are high and similar across the treatment regimens. This suggests that assuming patients were compliant to the medications concerned would have had little effect on the relative costs of the interventions. One problem with adjusting the cost estimates is that although patients may have not returned all the treatment packs, this may be because they had lost or disposed of the packs, which would therefore still have led to the same cost to the NHS.

Table 29. Compliance – pooled Adult data

Patient population	Statistic	Non-responder	Responder	Total
Mannitol				
rhDNase non-user	N	33	47	80
	Mean	91.91	81.29	85.67
	Median	95.10	87.40	90.75
rhDNase user	N	67	52	119
	Mean	82.97	84.06	83.45
	Median	90.70	88.60	89.60
Total	N	100	99	199
	Mean	85.92	82.74	84.34
	Median	92.25	88.00	89.70
Control				
rhDNase non-user	N	31	18	49
	Mean	94.13	94.40	94.23
	Median	94.90	95.15	95.10
rhDNase user	N	57	28	85
	Mean	84.32	84.88	84.51
	Median	94.40	89.35	90.50
Total	N	88	46	134
	Mean	87.78	88.61	88.06
	Median	94.65	92.75	94.05

***Note**: 6 outliers in the mannitol group with a reported compliance >200% were excluded.*

A sensitivity analysis has been done using the mean compliance rate of 85.67% for Mannitol monotherapy and 83.45% for Mannitol + rhDNase versus 84.41% for Control + rhDNase. Based on the observed effect that mean compliance is similar in responders and non-responders it was assumed that compliance has no effect on efficacy.

Table 30. Results sensitivity analysis reduced compliance

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) versus baseline (QALYs)
Control	180,188	11.40	9.75				
Mannitol	206,406	12.10	10.52	26,218	0.70	0.77	33,934
Control + rhDNase	238,740	11.40	9.75				
Mannitol + rhDNase	267,626	12.10	10.52	28,886	0.70	0.77	37,387
ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years							

B16. Please provide life years in specific health states for the comparators as basic outcome of the modeling exercise. (Chapter 6.7.9)

The disaggregated life years for Mannitol and Control are presented in Table 31.

Table 31. Summary of LY gain by health state

Health state	LY intervention (Mannitol)	LY comparator (Control)	Increment	Absolute increment	% absolute increment
CF with improved respiratory symptoms	*4.26*	*4.18*	*0.08*	*0.08*	*10%*
CF	*7.74*	*7.07*	*0.67*	*0.67*	*83%*
Lung transplant	*0.10*	*0.16*	*-0.06*	*0.06*	*7%*
Total	*12.10*	*11.40*	*0.70*	*0.81*	*100%*
LY, life years					

Section C – Clarification on literature searches

C1. Please provide further details regarding the search strategy presented in 9.4.4 (pg 220) in order for the ERG to replicate it. Section 9.4.1 states that Medline, Medline In-Process and Embase were searched via the Ovid host, however the strategy presented in 9.4.4 does not appear to be Ovid search syntax and did not work when put into Ovid Medline. Please clarify whether a PubMed search strategy was utilised, which databases were searched and which database hosts were used.

The databases searched for relevant information for indirect and mixed comparison were as follows:

- *Ovid EMBASE 1980 to 2010 Week 29*
- *Ovid MEDLINE(R) 1950 to July Week 3 2010*
- *Cochrane library (Wiley)*

The search strings used for the EMBASE and MEDLINE(R) searches are detailed in Table 32 and Table 33, respectively.

Table 32 Search strategy for the EMBASE search

#	Searches	Results
1	*exp cystic fibrosis/*	*33,077*
2	*(cystic* adj10 fibros*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]*	*38,816*
3	*mucoviscido*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]*	*2,118*
4	*exp mucociliary clearance/*	*2,349*
5	*(mucociliar* adj5 clear*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]*	*3,186*
6	*mucolytic.mp. or exp mucolytic agent/*	*45,313*
7	*(hyperton* adj5 saline).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]*	*4,495*
8	*hypertonic saline.mp. or exp sodium chloride/*	*87,491*
9	*exp hypertonic solution/*	*4,343*
10	*mannitol.mp. or exp MANNITOL/*	*24,671*

#	Searches	Results
11	mannitol.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	16
12	surface active agent.mp. or exp surfactant/	120,807
13	1 or 2 or 3 or 4 or 5	41,612
14	6 or 7 or 8 or 9 or 10 or 11 or 12	254,315
15	13 and 14	1,733
16	Clinical trial/	783,429
17	Randomized controlled trial/	265,029
18	Randomization/	50,841
19	Single blind procedure/	12,538
20	Double blind procedure/	94,656
21	Crossover procedure/	28,022
22	Placebo/	161,557
23	Randomi?ed controlled trial$.tw.	52,594
24	Rct.tw.	5,542
25	Random allocation.tw.	957
26	Randomly allocated.tw.	13,823
27	Allocated randomly.tw.	1,623
28	(allocated adj2 random).tw.	670
29	Single blind$.tw.	9,884
30	Double blind$.tw.	108,361
31	((treble or triple) adj blind$).tw.	206
32	Placebo$.tw.	144,443
33	Prospective study/	149,828
34	or/16-33	1,053,344
35	Case study/	9,659
36	Case report.tw.	188,625
37	Abstract report/ or letter/	746,230
38	or/35-37	941,074
39	34 not 38	1,022,188
40	15 and 39	443

Table 33 Search strategy for the MEDLINE(R) search

#	Searches	Results
1	exp Cystic Fibrosis/	24,492
2	(cystic* adj10 fibros*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	32,708
3	mucoviscido*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1,746
4	exp Mucociliary Clearance/	1,769
5	(mucociliar* adj5 clear*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2,781
6	mucolytic.mp. or exp Expectorants/	11,488
7	exp Hypertonic Solutions/ or exp Saline Solution, Hypertonic/	10,114
8	(hyperton* adj5 saline).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	6,441
9	saline solution.mp. or exp Sodium Chloride/	58,852
10	mannitol.mp. or exp Mannitol/	16,761
11	mannitol.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	0
12	surface active agent.mp. or exp Surface-Active Agents/	79,080
13	1 or 2 or 3 or 4 or 5	35,183
14	6 or 7 or 8 or 9 or 10 or 11 or 12	168,244
15	13 and 14	1,064
16	Randomized controlled trials as Topic/	68,394
17	Randomized controlled trial/	295,296
18	Random allocation/	69,192
19	Double blind method/	107,668
20	Single blind method/	14,244
21	Clinical trial/	463,526

#	Searches	Results
22	exp Clinical Trials as Topic/	231,239
23	or/16-22	748,047
24	(clinic$ adj trial$1).tw.	144,953
25	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	104,742
26	Placebos/	29,114
27	Placebo$.tw.	124,778
28	Randomly allocated.tw.	12,068
29	(allocated adj2 random).tw.	647
30	or/24-29	310,189
31	23 or 30	839,707
32	Case report.tw.	151,319
33	Letter/	684,911
34	Historical article/	266,318
35	Review of reported cases.pt.	0
36	Review, multicase.pt.	0
37	or/32-36	1,093,314
38	31 not 37	815,819
39	15 and 38	246

C2. Please provide complete search strategies for each of the databases searched (e.g. Medline, Medline In-Process, Embase, Cochrane Library etc.), including all search terms.

In addition to the searches detailed above, the following search was conducted in the Cochrane Library.

Table 34. **Search strategy for the Cochrane Library search**

#	Searches	Hits
1	MeSH descriptor Cystic Fibrosis explode all trees	927
2	cystic* NEAR/10 fibros*	2,408
3	mucoviscido*	54
4	MeSH descriptor Mucociliary Clearance explode all trees	161
5	mucociliar* NEAR/5 clear*	357
6	mucolytic	231
7	MeSH descriptor Expectorants explode all trees	807
8	MeSH descriptor Hypertonic Solutions explode all trees	467
9	MeSH descriptor Saline Solution, Hypertonic explode all trees	294
10	hyperton* NEAR/5 saline	606
11	saline solution	3,081
12	MeSH descriptor Sodium Chloride explode all trees	1,731
13	mannitol	746
14	MeSH descriptor Mannitol explode all trees	330
15	mannitol	2
16	surface active agent	712
17	MeSH descriptor Surface-Active Agents explode all trees	2,202
18	(#1 OR #2 OR #3 OR #4 OR #5)	2,698
19	(#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)	8,807
20	(#18 AND #19)	233

C3. Appendix 10 (page 227)

- Please clarify why the databases, Embase and EconLit were not searched.

Pharmaxis is aware that Embase covers approximately 2,040 journals not included in the PubMed database, nonetheless the latter includes more than 5,000 relevant journals, including the Journal of Cystic Fibrosis. As Pharmaxis does not have a direct access to Embase, it was decided not to prioritize the search in Embase database. However, for the relevant articles identified in the PubMed search the full article was read and the title of all cited references reviewed with the aim to identify additional articles.

Pharmaxis does not have access to the EconLit database, either. The search in the Cochrane Library, PubMed and the CRD databases (particularly the latter) should have provided all relevant economic publications and studies in cystic fibrosis.

- Please clarify why the PubMed searches were limited to English language only?

All the searches conducted in PubMed were first performed with language limited to English only. A second search was conducted for publications in French, German, Spanish, Italian or Dutch. Given the reduced number of articles in these languages (n=8 for the second search string; n=9 for the third search string) and that these studies were already covered by the English publications, it was decided to present the search of articles in English, only.

C4. Appendix 12 (page 233-4)

- Please clarify why the databases, Please clarify why, Embase, NHS EED and EconLit were not searched

The reasons for not conducting a search in the Embase and EconLit databases are the same as for C3.

We have now conducted a search on CRD database which includes NHS EED. The search strings used and the number of articles retrieved are provided in Table 35. The search has retrieved 71 articles but no additional studies on quality of life other than those described in Table 72 (Page 150) of the submission dossier.

Table 35. Search strategy for the CRD search

Database	Search	Hits
CRD (searched on March 25, 2011)	*(mannitol OR mannitol) AND (cystic fibrosis) AND ((quality of life) OR (utility OR utilities))*	*1*
CRD (searched on March 25, 2011)	*(cystic fibrosis) AND ((quality of life) OR (utility OR utilities))*	*71*

- Please clarify why the PubMed searches were limited to English language only?

  Like for the other appendices, all the searches conducted in PubMed were first performed with language limited to English only. A second search was conducted for publications in French, German, Spanish, Italian or Dutch. Twelve non English articles were identified. Of these, three reported the validation of the CFQ to different languages, two focused on children, three on screening and the other four were reviews. Thus, it was decided to present the search of articles in English, only.

- Please clarify why the PubMed search strategy reported as retrieving 177 references on page 234 but 119 references on page 148.

  The text in page 148 should have been modified as it relates to the initial literature search conducted on October 20, 2010 and which identified 119 references. The final list of studies (detailed in Table 72, page 150 of the submission dossier) was identified during the literature search conducted on December 31, 2010.

C5. Appendix 13 section 6.5 (pg 234-235).

- Please clarify why the databases, Embase and EconLit were not searched.

  The reasons for not conducting a search in the Embase and EconLit databases are the same as for C3 and C4.

- Please clarify why the PubMed searches were limited to English language only?

  All the searches conducted in PubMed were first performed with language limited to English only. A second search was conducted for publications in French, German, Spanish, Italian or Dutch. Two non English articles (both in French) were identified. Both articles were reviews and none provided any information on costs. Therefore, it was decided to present the search of articles in English, only.

Section D: Textual clarifications and additional points

D1. In Table 62, the relative risk of an exacerbation with mannitol (responders) is 0.66. In Table 56 the RR is 0.65, please clarify. (Chapter 6.3.6)

The value of 0.65 mentioned in Table 56 is correct. The calculated RR used in the model is 0.6547 (0.655 rounded to 3 decimals).

D2. In Table 71, please clarify whether the Standard Deviations presented are Standard Errors of the mean or observed standard deviations? (Chapter 6.4.3)

The presented standard deviations are observed standard deviations.

D3. Please clarify what is meant by "(0)" and "section 0" on page 32

The (0) on page 32 corresponds to Table 5. Section 0 corresponds to section 5.7.

D4. Please provide references for the studies identified in Appendix 4 and 5.

The references for the studies with mannitol listed in Appendix 4 and 5 are as follows:

- *Abstract 95: Randomised, double blind, placebo-controlled Phase III Study of Mannitol (inhaled dry powder mannitol) in Cystic Fibrosis (CF) – D. Bilton (UK).* The 32nd ECFS Conference.

- *Jaques A, Daviskas E, Turton JA, McKay K, Cooper P, Stirling RG, Robertson CF, Bye PT, Lesouëf PN, Shadbolt B, Anderson SD, Charlton B. Inhaled mannitol improves lung function in cystic fibrosis. Chest. 2008 Jun;133(6):1388-96. Epub 2008 Mar 13.*

The references for the studies with hypertonic saline listed in Appendix 4 and 5 are as follows:

- *Eng PA, Morton J, Douglass JA, Riedler J, Wilson J, Robertson CF. Short-term efficacy of ultrasonically nebulized hypertonic saline in cystic fibrosis. Pediatr Pulmonol. 1996 Feb;21(2):77-83.*
- *Riedler J, Reade T, Button B, Robertson CF. Inhaled hypertonic saline increases sputum expectoration in cystic fibrosis. J Paediatr Child Health. 1996 Feb;32(1):48-50.*
- *Button BM, Riedler J, Eng P,RobertsonCF. Inhaled hypertonic saline as an adjunct to chest physiotherapy in cystic fibrosis; the three year clinical experience [abstract]. Pediatric Pulmonology 1996;Suppl 13: 306.*

- *Chadwick SL, Moss SJ, Bott J, Geddes DM, Alton EWFW. Effect of hypertonic , isotonic saline and water challenges on the airways of cystic fibrosis patients [abstract]. Thorax 1997;52(Suppl 6):A43.*
- *Robinson M, Regnis J, Bailey DL, King M, Bautovich G, Bye PTP. The effects of hypertonic saline, amiloride and cough on mucociliary clearance in patients with cystic fibrosis. American Journal of Respiratory and Critical Care Medicine 1996;153:1503-9.*
- *Robinson M, Hemming A, Regnis J,Wong A, Bailey D, Bautotvich G, et al. Effect of increasing doses of hypertonic saline on mucociliary clearance inpatients with cystic fibrosis. Thorax 1997;52(10):900-3.*
- *Robinson M, Daviskas E, Eberl S, Baker J, Chan H, Anderson, S, et al. The effect of inhaled mannitol on bronchial mucus clearance in cystic fibrosis patients: a pilot study. European Respiratory Journal 1999;14:678-85.*
- *Elkins MR, Robinson M, Rose BR, Harbour C, Moriarty CP, Marks GB, Belousova EG, Xuan W, Bye PT; National Hypertonic Saline in Cystic Fibrosis (NHSCF) Study Group. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. N Engl J Med. 2006 Jan 19;354(3):229-40.*

Appendix A: Linear regression models

1. OUTCOME

Linear regression analysis was performed on the following continuous outcome:

fev1p_locf= FEV1 percentage predicted at visit 4 allowing for growth.

Missing values were replaced by the last observed values, that is, if FEV_1 value is missing at visit 4 but available at visit 3 / visit 2 then the values from visit 3 / visit 2 will be used as the outcome.

The derivation of the FEV_1 predicted at visit 4 allowing for growth is presented in the SAP and the Analysis of FEV_1 as percent predicted allowing for growth.PDF file.

2. PREDICTORS

Prognostic factors have been identified among the following variables:

- *Age at baseline (continuous)=age*
- *Treatment group (1=Mannitol / 0=Control)=trtgroup*
- *FEV1 percentage predicted at visit 1 (continuous)= fev1p_imp1*
- *Gender (1=Male / 0=Female)=gender*
- *BMI at visit 1 (continuous)= BMI_v1*
- *Total number of PDPE during DBP (continuous)= nb_PDPE_DBP*
- *Had any PDPE during DBP (1=Yes / 0=No)= hadpe_DBP*
- *Pseudomonas aeruginosa (mucoid) infection during DBP (1=Yes / 0=No)=pa*
- *Burkholderia cepacia infection during DBP (1=Yes / 0=No)=bcc*
- *Staphylococcus aureus infection during DBP (1=Yes / 0=No)=staph*
- *Pain* reported during DBP (1=Yes / 0=No)=pain*
- *Pharyngolaryngeal pain reported during DBP (1=Yes / 0=No)=phary*
- *Respiratory symptoms (1=Improved / 0=Not improved)=resp4*
- *Vitality (1=Improved / 0=Not improved)=vit*
- *Physical symptoms (1=Improved / 0=Not improved)=phys*
- *Responder (1=Responder/0=Non-responder)=resp*

** Pain is defined as follows: if the preferred term of the reported adverse event contains the word "pain" or headache.*

To be noted that for the respiratory symptoms, vitality and the physical symptoms variables the minimal clinical important difference (MCID) was used to determine the categories as follows: the change from baseline at visit V4 score is compared to the MCID values. The following MCID values were used:

- *Respiratory symptoms: MCID=4 (based on the Quitner paper)*
- *Vitality: MCID=8.6*
- *Physical symptoms: MCID=8.4*

3. METHOD

Firstly, univariate analysis was performed using PROC TTEST (for categorical variables) and PROC CORR (for continuous variables) in SAS.

Next, multiple regression analysis was performed using PROC REG in SAS. All variables significant at a 0.5 significance level in the univariate analysis were included in the multivariate analysis. A backward procedure was carried out. The backward elimination technique begins by calculating F statistics for a model, including all of the independent variables. Then the variables are deleted from the model one by one until all the variables remaining in the model produce F statistics significant at the 0.05 level. At each step, the variable showing the smallest contribution to the model is deleted.

Only main effects are considered and no interaction between the independent variables.

For the validation of the model, P-value and R-square value were investigated to measure goodness-of-fit. To test the adequacy of the model we performed a residual analysis. We examined the final regression model for multicollinearity, because a high degree of multicollinearity makes the parameter estimates in the model not stable. Multicollinearity exists whenever an independent variable is highly correlated with one or more of the other independent variables and it can be detected by using the variance inflation factors (VIF) values. VIF larger than 10 implies serious problems with multicollinearity.

4. RESULTS

4.1 Univariate Analysis

4.1.1. rhDNase users

The analysis was performed on the intent-to-treat patient population (ITT), adults and rhDNase users on the pooled 301 and 302 study populations. There are 207 patients in this subset.

The Pearson correlation coefficients, the p-value and the number of observations are presented in Table 1 for the continuous variables.

Table 36. Pearson correlation coefficients, the p-value and the number of observations – Adults rhDNase users

	AGE (Age in Years at Baseline)	**bmi_v1 (BMI (kg/m²) at V1)**	**fev1p_imp1 (% predicted FEV1 (Imputed) at V1)**	**nb_PDPE_DBP (Number of PDPE in DBP)**
fev1p_locf (% predicted FEV1 (Imputed) at V4 – LOCF)	*-0.18289* *0.0113* *191*	*0.13935* *0.0545* *191*	*0.89127* *<.0001* *191*	*-0.30747* *<.0001* *191*

The results of the t-test for the categorical variables are presented in Table 2.

Table 37. FEV1 % predicted at visit 4 by different categorical variables – Adults rhDNase users

Variable	N	Mean[SD]	95% CI	p-value
Treatment group				0.0619
Control	80	55.34 [17.091]	[51.532; 59.139]	
Mannitol	111	60.04 [17.079]	[56.829; 63.254]	
Gender				0.9427
Female	87	58.17 [16.647]	[54.621; 61.716]	
Male	104	57.99 [17.724]	[54.541; 61.435]	
PDPE during DBP				<.0001
No	147	60.92 [16.778]	[58.184; 63.654]	
Yes	44	48.55 [15.181]	[43.938; 53.169]	
PA infection during DBP				0.2012
No	78	59.99 [18.106]	[55.906; 64.070]	
Yes	113	56.75 [16.492]	[53.673; 59.821]	
BCC infection during DBP				0.4357
No	177	58.34 [17.112]	[55.806; 60.882]	
Yes	14	54.61 [18.547]	[43.902; 65.320]	
Staphylococcus infection during DBP				0.2952
No	114	57.00 [17.689]	[53.715; 60.280]	
Yes	77	59.66 [16.426]	[55.931; 63.388]	
Pain during DBP				0.5035
No	124	57.46 [17.175]	[54.403; 60.509]	
Yes	67	59.21 [17.309]	[54.985; 63.429]	
Pharyngolaryngeal pain				0.9873
No	178	58.08 [17.236]	[55.526; 60.625]	
Yes	13	58.00 [17.342]	[47.517; 68.476]	
Respiratory Symptoms				0.0472
Not improved	114	57.21 [16.421]	[54.167; 60.261]	
Improved	64	62.44 [17.331]	[58.114; 66.772]	
Vitality				0.5548
Not improved	152	58.67 [16.564]	[56.016; 61.325]	
Improved	27	60.76 [18.967]	[53.261; 68.267]	
Physical symptoms				0.3591
Not improved	158	58.56 [16.759]	[55.929; 61.196]	
Improved	21	62.17 [18.085]	[53.943; 70.407]	
Responder				0.2893
Non-responder	110	56.94 [18.329]	[53.472; 60.400]	
Responder	81	59.61 [15.506]	[56.182; 63.039]	

4.1.2 Univariate Analysis rhDNase non-users

The analysis was performed on the intent-to-treat patient population (ITT), adults and rhDNase non-users on the pooled 301 and 302 study populations. There are 134 patients in this subset.

The Pearson correlation coefficients, the p-value and the number of observations are presented in Table 3 for the continuous variables.

Table 38. Pearson correlation coefficients, the p-value and the number of observations – Adults rhDNase non-users

	AGE (Age in Years at Baseline)	**bmi_v1 (BMI (kg/m²) at V1)**	**fev1p_imp1 (% predicted FEV1 (Imputed) at V1)**	**nb_PDPE_DBP (Number of PDPE in DBP)**
fev1p_locf (% predicted FEV1 (Imputed) at V4 – LOCF)	*-0.09314* *0.2996* *126*	*0.21787* *0.0143* *126*	*0.86858* *<.0001* *126*	*-0.22693* *0.0106* *126*

The results of the t-test for the categorical variables are presented in Table 4.

Table 39. FEV1 % predicted at visit 4 by different categorical variables – Adults rhDNase non-users

Variable	**N**	**Mean[SD]**	**95% CI**	**p-value**
Treatment group				*0.0928*
Control	*49*	*61.11 [16.783]*	*[56.289; 65.930]*	
Mannitol	*77*	*65.75 [13.758]*	*[62.631; 68.876]*	
Gender				*0.7118*
Female	*50*	*63.33 [14.495]*	*[59.211; 67.450]*	
Male	*76*	*64.35 [15.588]*	*[60.791; 67.915]*	
PDPE during DBP				*0.0525*
No	*98*	*65.34 [14.838]*	*[62.366; 68.316]*	
Yes	*28*	*59.07 [15.322]*	*[53.129; 65.012]*	
PA infection during DBP				*0.0029*
No	*50*	*68.83 [13.581]*	*[64.974; 72.693]*	
Yes	*76*	*60.73 [15.290]*	*[57.239; 64.227]*	
BCC infection during DBP				*0.2444*
No	*113*	*63.41 [15.332]*	*[60.557; 66.272]*	
Yes	*13*	*68.58 [12.619]*	*[60.958; 76.209]*	
Staphylococcus infection during DBP				*0.1461*
No	*73*	*65.62 [15.598]*	*[61.979; 69.257]*	
Yes	*53*	*61.65 [14.243]*	*[57.721; 65.573]*	
Pain during DBP				*0.9299*
No	*77*	*63.85 [15.984]*	*[60.225; 67.481]*	
Yes	*49*	*64.10 [13.792]*	*[60.135; 68.059]*	
Pharyngolaryngeal pain				*0.7023*
No	*112*	*63.76 [15.334]*	*[60.894; 66.636]*	
Yes	*14*	*65.41 [13.637]*	*[57.537; 73.285]*	
Respiratory Symptoms				*0.4494*
Not improved	*63*	*62.97 [14.996]*	*[59.194; 66.747]*	

Variable	N	Mean[SD]	95% CI	p-value
Improved	50	65.15 [15.343]	[60.788; 69.509]	
Vitality				0.0772
Not improved	88	62.59 [15.700]	[59.268; 65.921]	
Improved	25	68.65 [11.995]	[63.698; 73.600]	
Physical symptoms				0.7277
Not improved	92	64.17 [15.222]	[61.020; 67.325]	
Improved	21	62.89 [14.995]	[56.065; 69.717]	
Responder				0.0377
Non-responder	61	61.07 [15.908]	[56.994; 65.142]	
Responder	65	66.65 [13.912]	[63.203; 70.097]	

4.1.3 Univariate Analysis rhDNase non-users unsuitable to rhDNase

The analysis was performed on the intent-to-treat patient population (ITT), adults and rhDNase nonusers unsuitable to take rhDNase on the pooled 301 and 302 study populations. There are 65 patients in this subset.

The Pearson correlation coefficients, the p-value and the number of observations are presented in Table 5 for the continuous variables.

Table 40. Pearson correlation coefficients, the p-value and the number of observations – Adults rhDNase non-users unsuitable to take rhDNase.

	AGE	bmi_v1	fev1p_imp1	nb_PDPE_DBP
fev1p_locf % predicted FEV1 (Imputed) at V4 - LOCF	-0.07622 0.5527 63	0.24322 0.0548 63	0.85013 <.0001 63	-0.18953 0.1368 63

The results of the t-test for the categorical variables are presented in Table 6.

Table 41. FEV1 % predicted at visit 4 by different categorical variables – Adults rhDNase non-users unsuitable to take rhDNase.

Variable	N	Mean[SD]	95% CI	p-value (t-test)	p-value (Wilcoxon)
Treatment group				0.0024	0.0031
Control	20	55.00 [13.951]	[48.472; 61.530]		
Mannitol	43	66.53 [13.210]	[62.467; 70.597]		
Gender				0.1138	0.1535
Female	29	59.76 [13.453]	[54.643; 64.877]		
Male	34	65.52 [14.827]	[60.351; 70.698]		
PDPE during DBP				0.1237	0.1624
No	49	64.37 [14.954]	[60.072; 68.662]		
Yes	14	57.64 [11.148]	[51.199; 64.073]		
PA infection during DBP				0.1442	0.1212
No	24	66.26 [14.854]	[59.986; 72.530]		
Yes	39	60.79 [13.882]	[56.287; 65.287]		
BCC infection during DBP				0.1855	0.2166
No	56	62.02 [14.259]	[58.200; 65.837]		
Yes	7	69.70 [14.679]	[56.120; 83.271]		
Staphylococcus infection during DBP				0.2165	0.2567
No	32	65.09 [15.071]	[59.656; 70.524]		
Yes	31	60.58 [13.517]	[55.623; 65.539]		
Pain during DBP				0.4508	0.3983
No	37	64.03 [14.912]	[59.057; 69.001]		
Yes	26	61.22 [13.736]	[55.676; 66.772]		
Pharyngolaryngeal pain				0.4109	0.4638
No	56	62.34 [14.129]	[58.555; 66.123]		
Yes	7	67.13 [16.927]	[51.474; 82.784]		
Respiratory Symptoms				0.8261	0.8808
Not improved	34	63.18 [15.449]	[57.786; 68.567]		
Improved	24	62.34 [12.322]	[57.135; 67.541]		
Vitality				0.5487	0.4729
Not improved	44	62.19 [15.351]	[57.528; 66.862]		
Improved	14	64.83 [9.493]	[59.344; 70.306]		
Physical symptoms				0.6265	0.5204
Not improved	50	62.46 [14.603]	[58.314; 66.614]		
Improved	8	65.11 [11.212]	[55.741; 74.488]		
Responder				0.8979	0.8505
Non-responder	26	63.15 [15.513]	[56.886; 69.418]		
Responder	37	62.67 [13.766]	[58.084; 67.264]		

4.2 Multivariate Analysis

As indicated in section 3, the multivariate regression model included only the variables which were significant at the significance level of 0.5 in the univariate analysis.

4.2.1. rhDNase users

The following variables were included in the multivariate model:

Quantitative:

- *Age at baseline (continuous)=age*
- *BMI at visit 1 (continuous)= BMI_v1*
- *FEV1 percentage predicted at visit 1 (continuous)= fev1p_imp1*
- *Total number of PDPE during DBP (continuous)= nb_PDPE_DBP*

Qualitative:

- *Treatment group (1=Mannitol / 0=Control)=trtgroup*
- *Had any PDPE during DBP (1=Yes / 0=No)= hadpe_DBP*
- *Pseudomonas aeruginosa (mucoid) infection during DBP (1=Yes / 0=No)=pa*
- *Burkholderia cepacia infection during DBP (1=Yes / 0=No)=bcc*
- *Staphylococcus aureus infection during DBP (1=Yes / 0=No)=staph*
- *Respiratory symptoms (1=Improved / 0=Not improved)=resp4*
- *Physical symptoms (1=Improved / 0=Not improved)=phys*
- *Responder (1=Yes / 0=No)=resp*

The treatment group variable was forced into the model, although it was not significant in the univariate analysis.

Five steps were necessary to obtain the final model. 178 observations had been used from the 207 in total. Treatment group was forced into the model. The final model includes the treatment group, FEV1 percentage predicted at visit 1 and being a responder. The parameter estimates, p-values and the variance inflation factor are given in Table 7 below.

All predictors in the model are significant at level 0.05, and adjusted R-square of the model is 0.81 which means 81% of the variation in the dependent variable was accounted by the explanatory variables. The variance inflation factor (VIF) values do not suggest multicollinearity between predictors.

Table 42. Model for FEV1 percentage predicted at visit 4 allowing for growth - Adults rhDNase users

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	Variance Inflation
Intercept	*1*	*0.37894*	*2.30340*	*0.16*	*0.8695*	*0*
Treatment group(1=Mannitol/0=Control)	*1*	*2.54392*	*1.14672*	*2.22*	*0.0278*	*1.02036*
% predicted FEV1 (Imputed) at V1	*1*	*0.93803*	*0.03533*	*26.55*	*<.0001*	*1.02526*
Responder	*1*	*4.55343*	*1.15195*	*3.95*	*0.0001*	*1.03301*

Residual analysis was performed. A graphical examination indicates that the model is adequate and that the normality and linear pattern assumptions are not severely violated.

Figure 5. Histogram of the residuals for Model 2- ADULTS rhDNase non-users

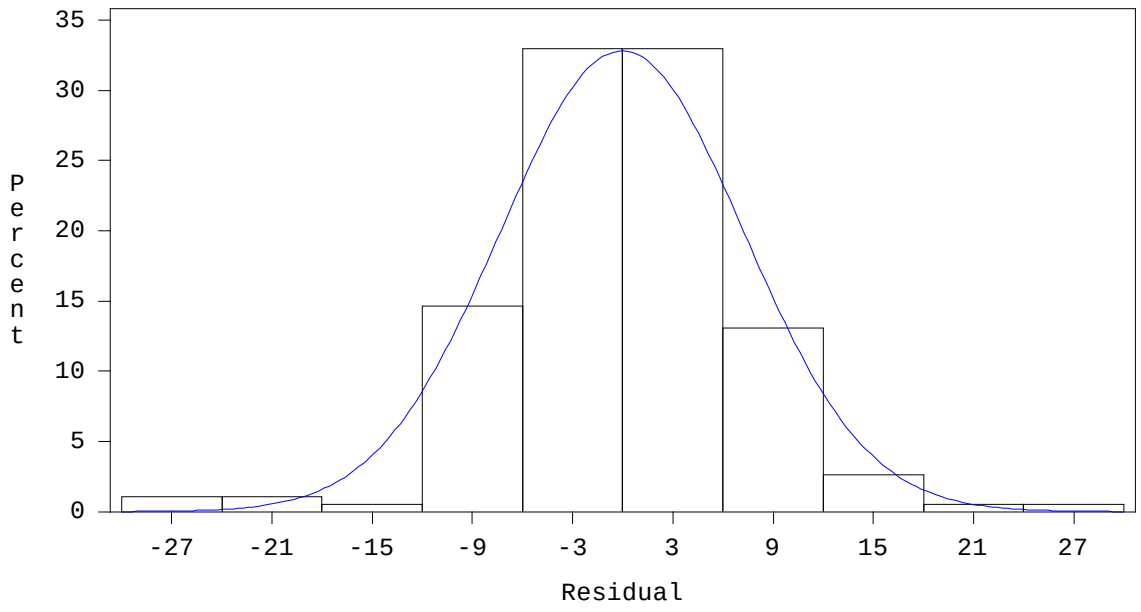
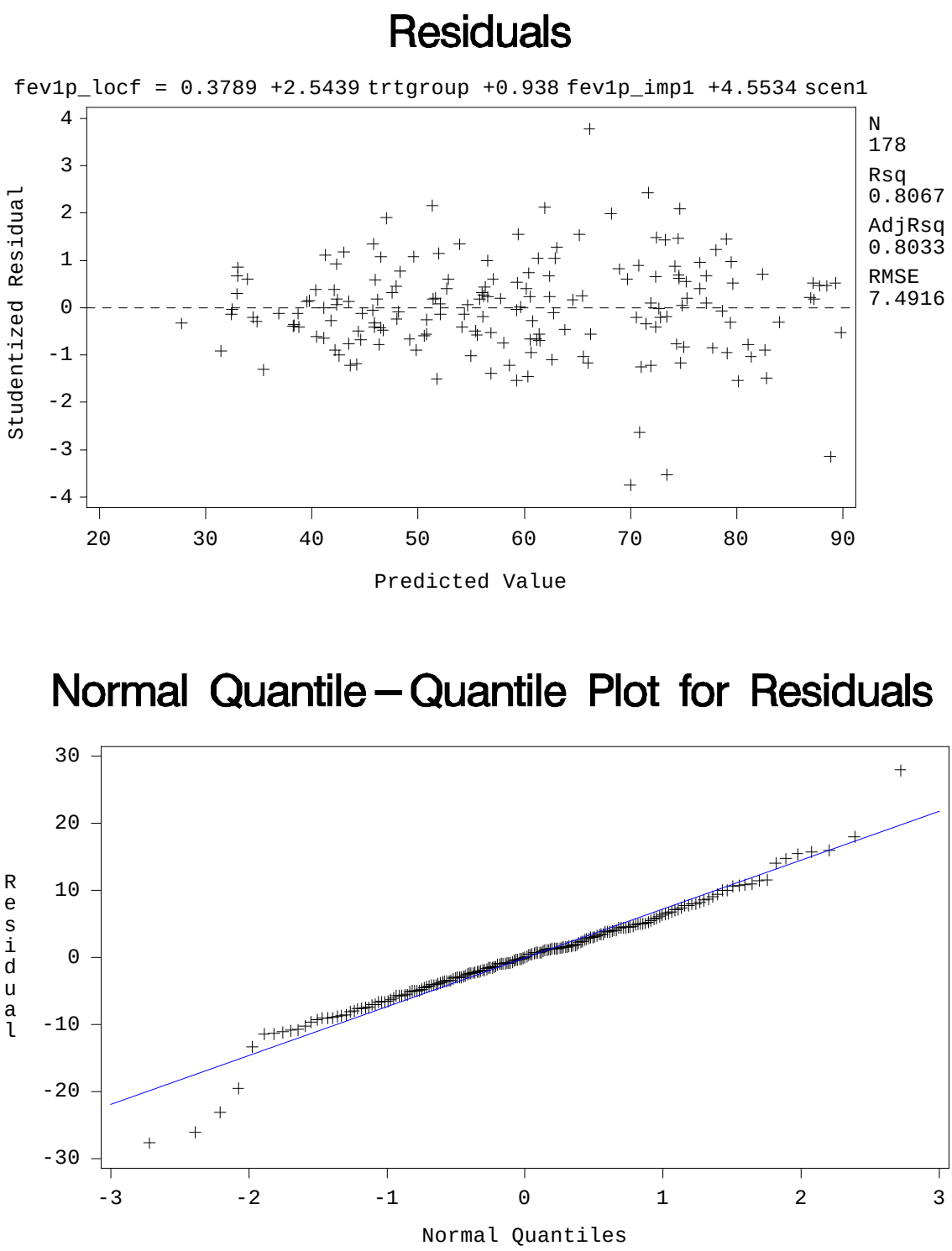


Table 43. Covariance matrix for Model for FEV1 percentage predicted at visit 4 allowing for growth – Adults rhDNase users

Variable	Intercept	trtgroup	fev1p_imp1	Base case
Intercept	*5.306*	*-0.476*	*-0.074*	*-0.818*
Treatment group(1=Mannitol/0=Control)	*-0.476*	*1.315*	*-0.004*	*-0.162*
% predicted FEV1 (Imputed) at V1	*-0.074*	*-0.004*	*0.001*	*0.006*
Responder	*-0.818*	*-0.162*	*0.006*	*1.327*

Figure 6. Residual plots for Model - Adults rhDNase users



4.2.2. rhDNase non-users

The following variables were included in the multivariate model:

Quantitative:

- *Age at baseline (continuous)=age*
- *BMI at visit 1 (continuous)= BMI_v1*
- *FEV1 percentage predicted at visit 1 (continuous)= fev1p_imp1*
- *Total number of PDPE during DBP (continuous)= nb_PDPE_DBP*

Qualitative:

- *Treatment group (1=Mannitol / 0=Control)=trtgroup*
- *Had any PDPE during DBP (1=Yes / 0=No)= hadpe_DBP*
- *Pseudomonas aeruginosa (mucoid) infection during DBP (1=Yes / 0=No)=pa*
- *Burkholderia cepacia infection during DBP (1=Yes / 0=No)=bcc*
- *Staphylococcus aureus infection during DBP (1=Yes / 0=No)=staph*
- *Respiratory symptoms (1=Improved / 0=Not improved)=resp4*
- *Vitality (1=Improved / 0=Not improved)=vit*
- *Responder (1=Yes / 0=No)=resp*

The treatment group variable was forced into the model, although it was not significant in the univariate analysis.

Six steps were necessary to obtain the final model. 126 observations had been used from the 134 in total. The final model includes treatment group, Staphylococcus aureus infection in DBP, BMI at visit 1, FEV1 percentage predicted at visit 1, number of PDPE in DBP and being a responder. The parameter estimates, p-values and the variance inflation factor are given in Table 9 below.

All predictors in the model except treatment group are significant at level 0.05, and adjusted R-square of the model is 0.812 which means 81.2% of the variation in the dependent variable was accounted by the explanatory variables. The variance inflation factor (VIF) values do not suggest multicollinearity between predictors.

Table 44. Model for FEV1 percentage predicted at visit 4 allowing for growth - Adults rhDNase non-users

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	Variance Inflation
Intercept	1	-4.22732	5.10268	-0.83	0.4093	0
Treatment group(1=Mannitol/0=Control)	1	0.18901	1.33851	0.14	0.8880	1.06780
Staphylococcus aureus infection in DBP	1	-2.69997	1.31511	-2.05	0.0425	1.06515
BMI (kg/m²) at V1	1	0.44400	0.18766	2.37	0.0198	1.04103
% predicted FEV1 (Imputed) at V1	1	0.91100	0.04663	19.54	<.0001	1.05011
Number of PDPE in DBP	1	-2.83534	1.19011	-2.38	0.0190	1.07533
Responder	1	6.06891	1.33061	4.56	<.0001	1.09869

Residual analysis was performed. A graphical examination indicates that the model is adequate and that the normality and linear pattern assumptions are not violated.

Figure 7. Histogram of the residuals for Model - ADULTS rhDNase non-users

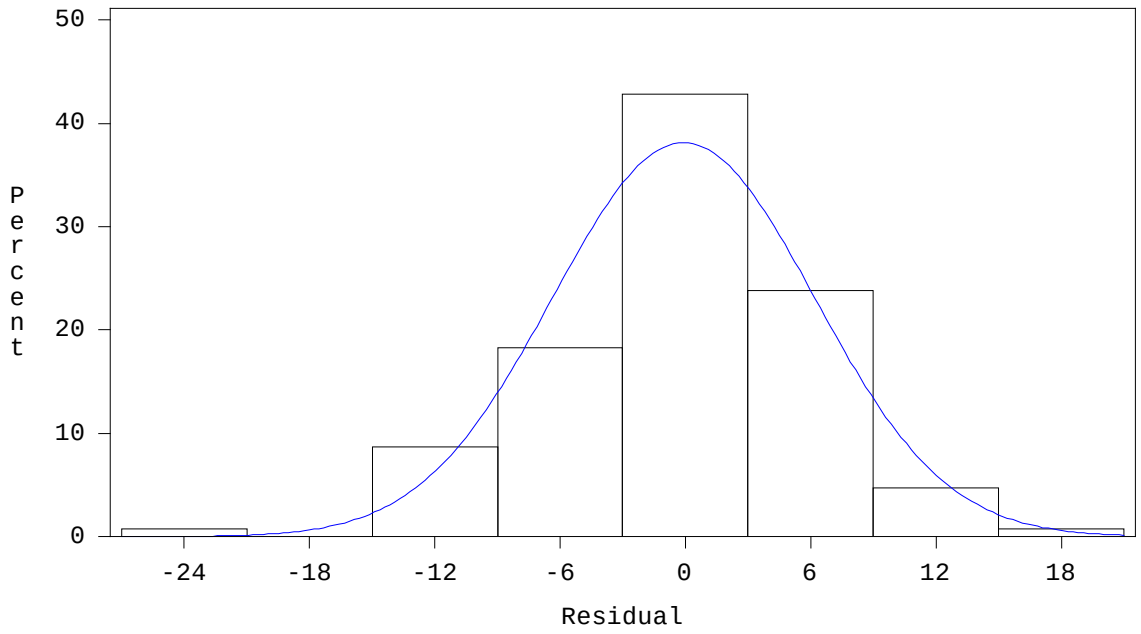
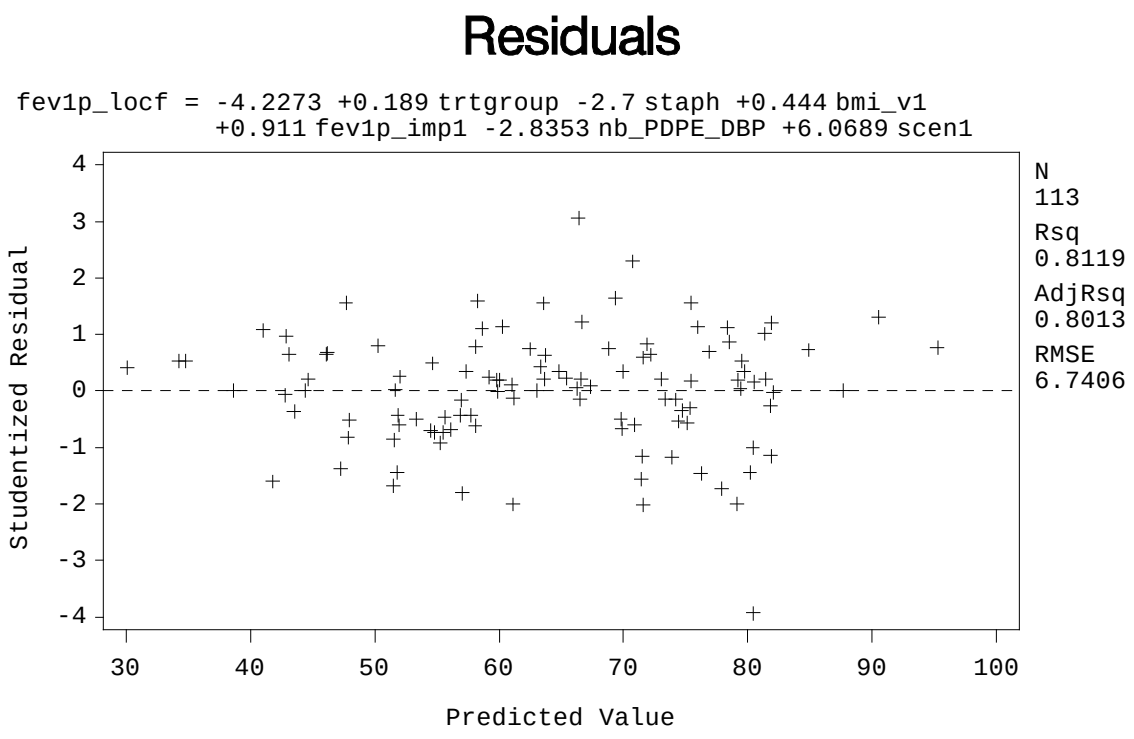
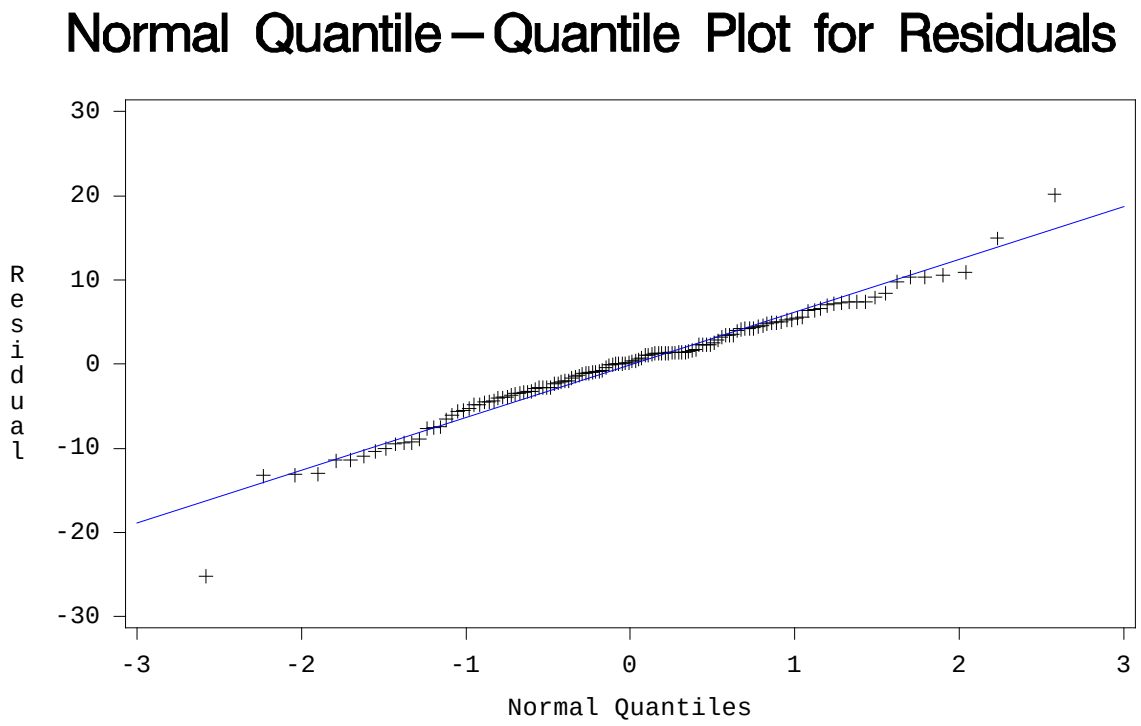


Table 45. Covariance matrix for Model 2 for FEV1 percentage predicted at visit 4 allowing for growth – Adults rhDNase non-users

Variable	Intercept	trtgroup	bmi_v1	fev1p_imp1	nb_PDPE_DBP	resp
Intercept	*21.082*	*-0.274*	*-0.626*	*-0.092*	*-0.817*	*-0.724*
Treatment group(1=Mannitol/0=Control)	*-0.274*	*1.541*	*-0.012*	*-0.004*	*0.085*	*-0.340*
BMI (kg/m²) at V1	*-0.626*	*-0.012*	*0.031*	*-0.001*	*-0.003*	*-0.008*
% predicted FEV1 (Imputed) at V1	*-0.092*	*-0.004*	*-0.001*	*0.002*	*0.006*	*0.005*
Number of PDPE in DBP	*-0.817*	*0.085*	*-0.003*	*0.006*	*1.235*	*0.245*
Responder	*-0.724*	*-0.340*	*-0.008*	*0.005*	*0.245*	*1.501*

Figure 8. Residual plots for Model - Adults rhDNase non-users





4.2.3. rhDNase non-users unsuitable to rhDNase

The following variables were included in the multivariate model:

Quantitative:

- *BMI at visit 1 (continuous)= BMI_v1*
- *FEV1 percentage predicted at visit 1 (continuous)= fev1p_imp1*
- *Total number of PDPE during DBP (continuous)= nb_PDPE_DBP*

Qualitative:

- *Treatment group (1=Mannitol / 0=Control)=trtgroup*
- *Gender (1=Male / 0=Female)=gender*
- *Had any PDPE during DBP (1=Yes / 0=No)= hadpe_DBP*
- *Pseudomonas aeruginosa (mucoid) infection during DBP (1=Yes / 0=No)=pa*
- *Burkholderia cepacia infection during DBP (1=Yes / 0=No)=bcc*
- *Staphylococcus aureus infection during DBP (1=Yes / 0=No)=staph*
- *Pain* reported during DBP (1=Yes / 0=No)=pain*
- *Pharyngolaryngeal pain reported during DBP (1=Yes / 0=No)=phary*

In addition to the variables mentioned above, the responder variable was considered into the model.

Six steps were necessary to obtain the final model. 63 observations had been used from the 65 in total. The final model includes treatment group, BMI (kg/m²) at visit 1, FEV1 percentage predicted at visit 1 and being a responder. The parameter estimates, p-values and the variance inflation factor are given in Table 11 below.

All predictors in the model are significant at level 0.05, and adjusted R-square of the model is 0.826 which means 82.6% of the variation in the dependent variable was accounted by the explanatory variables. The variance inflation factor (VIF) values do not suggest multicollinearity between predictors.

Table 46. Model for FEV1 percentage predicted at visit 4 allowing for growth - Adults rhDNase non-users unsuitable to take rhDNase.

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	Variance Inflation
Intercept	1	-9.61818	6.34653	-1.52	0.1351	0
Treatment group(1=Mannitol/0=Control)	1	4.08532	1.88607	2.17	0.0344	1.19132
BMI (kg/m²) at V1	1	0.70306	0.22490	3.13	0.0028	1.01019
% predicted FEV1 (Imputed) at V1	1	0.82660	0.05978	13.83	<.0001	1.20155
Responder	1	5.43466	1.80366	3.01	0.0038	1.21872

Residual analysis was performed. A graphical examination indicates that the model is adequate and that the normality and linear pattern assumptions are not violated.

Figure 9. *Histogram of the residuals for Model - Adults rhDNase non-users unsuitable to take rhDNase.*

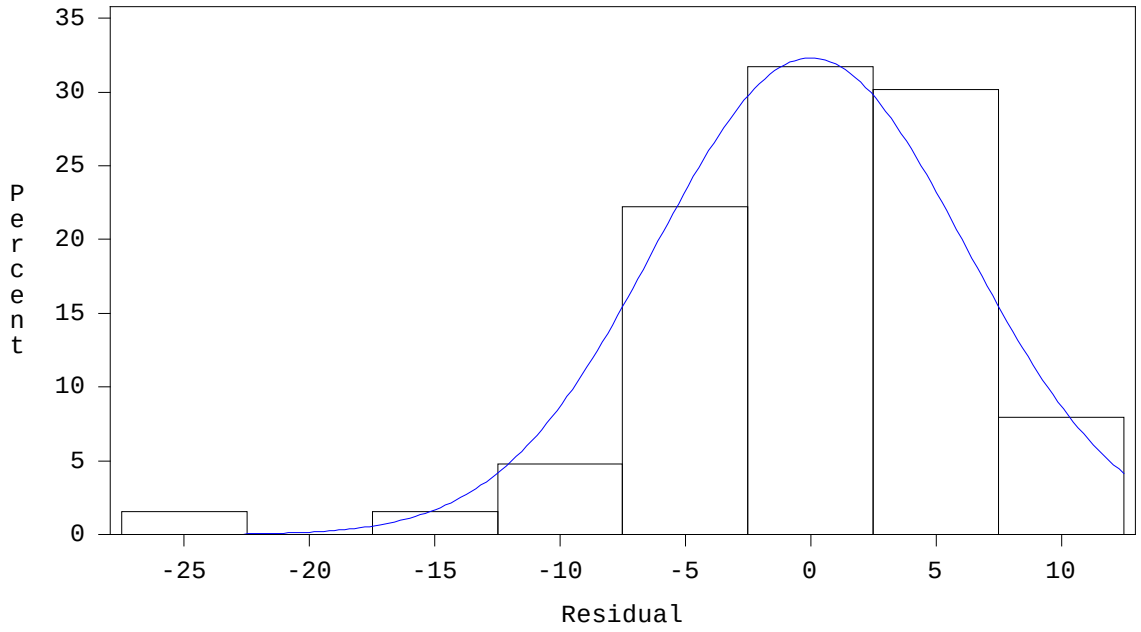
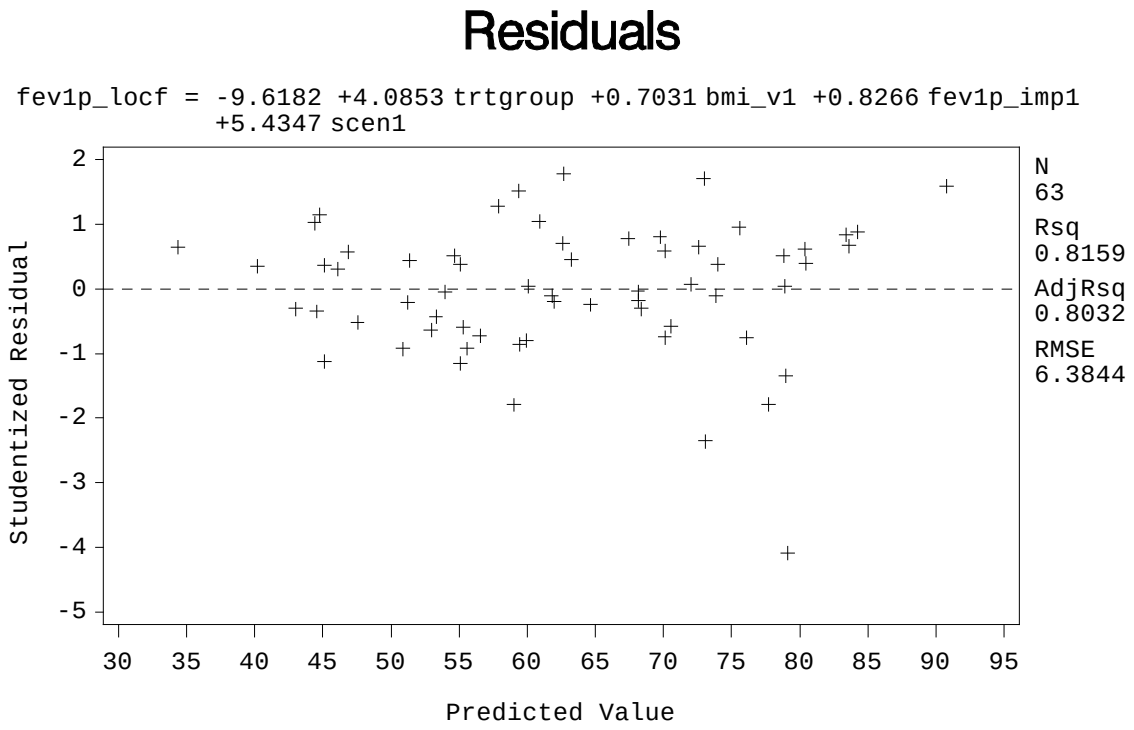
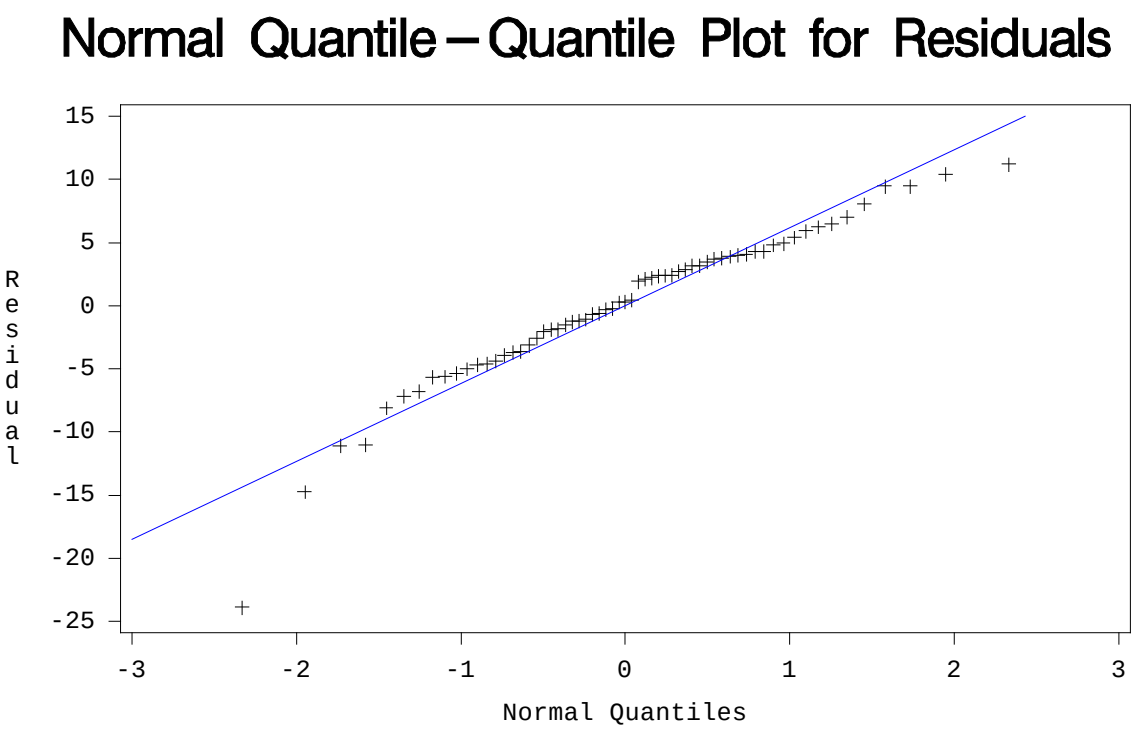


Table 47. Covariance matrix for Model for FEV1 percentage predicted at visit 4 allowing for growth – Adults rhDNase non-users unsuitable to take rhDNase.

Variable	*Intercept*	*trtgroup*	*bmi_v1*	*fev1p_imp1*	*scen1*
Intercept	*40.279*	*0.441*	*-1.124*	*-0.192*	*-3.745*
Treatment group(1=Mannitol/0=Control)	*0.441*	*3.557*	*-0.001*	*-0.036*	*-1.156*
BMI (kg/m²) at V1	*-1.124*	*-0.001*	*0.051*	*-0.001*	*0.017*
% predicted FEV1 (Imputed) at V1	*-0.192*	*-0.036*	*-0.001*	*0.004*	*0.037*
Responder	*-3.745*	*-1.156*	*0.017*	*0.037*	*3.253*

Figure 10. Residual plots for Model - Adults rhDNase non-users unsuitable to take rhDNase.





Appendix B: Protocol Defined Pulmonary Exacerbations by RhDNase Use and Reason for RhDNase Non-Use - Rate Ratio

Model Term (Analysed: N=600)	Estimate	Standard Error	Rate Ratio	95% Confidence Interval	Estimate P-value	Type III Effect P-value
Treatment (mannitol versus control)	-0.31	0.23	0.73	(0.47, 1.15)	0.176	0.176
Treatment by RhDNase use and Reason for RhDNase Non-Use						0.315
Intolerant/did not respond/not eligible	-0.35	0.51	0.70	(0.26, 1.90)	0.486	
All other non-users	-0.61	0.40	0.54	(0.25, 1.20)	0.131	
Users	0.04	0.20	1.04	(0.71, 1.52)	0.856	
Treatment by Project						0.586
CF-301	-0.40	0.26	0.67	(0.41, 1.11)	0.117	
CF-302	-0.22	0.31	0.80	(0.44, 1.47)	0.481	
Disease severity at baseline	-0.04	0.01	0.96	(0.95, 0.97)	<.001	<.001
RhDNase use and Reason for RhDNase Non-Use						0.204
Intolerant/did not respond/not eligible versus Users	-0.36	0.28	0.70	(0.40, 1.21)	0.198	
All other non-users versus Users	0.22	0.24	1.24	(0.78, 1.98)	0.357	
Age	-0.02	0.01	0.98	(0.97, 1.00)	0.084	0.084
Country within project						0.007
Australia/New Zealand versus UK/Republic of Ireland	0.07	0.23	1.08	(0.69, 1.69)	0.751	
Argentina versus USA	-1.55	0.42	0.21	(0.09, 0.48)	<.001	
Belgium/The Netherlands versus USA	-0.75	0.54	0.47	(0.17, 1.35)	0.162	
Canada versus USA	-0.41	0.49	0.67	(0.26, 1.74)	0.406	
France versus USA	-0.47	0.45	0.62	(0.26, 1.52)	0.298	
Germany versus USA	-1.53	0.73	0.22	(0.05, 0.91)	0.036	
Gender (male versus female)	-0.32	0.17	0.73	(0.52, 1.02)	0.064	0.064
Project (CF-301 versus CF-302)	0.76	0.23	2.14	(1.37, 3.33)	<.001	<.001

Protocol(s): DPM-CF-301 & DPM-CF-302
Analysis: Intent to Treat Population

Appendix C: Univariate analysis 6-month treatment cost

1. OUTCOME

A univariate analysis was performed in order to identify possible significant factors associated with the total costs per patient in the adult pooled 301/302 population with no PDPE's during blinded phase.

For the FEV1 percentage predicted at visit 4 allowing for growth (fev1p_locf) variable the following imputation method has been used: Missing values were replaced by the last observed values, that is, if FEV1 value is missing at visit 4 but available at visit 3 / visit 2 then the values from visit 3 / visit 2 will be used.

The derivation of the FEV_1 predicted at visit 4 allowing for growth is presented in the SAP and the Analysis of FEV_1 as percent predicted allowing for growth.PDF file.

2. PROGNOSTIC FACTORS

Prognostic factors have been identified among the following variables:

- *Age at baseline (continuous)=age*
- *Treatment group (1=Mannitol / 0=Control)=trtgroup*
- *FEV1 percentage predicted at visit 1 (continuous)= fev1p_imp1*
- *FEV1 percentage predicted at visit 4 (continuous)= fev1p_ locf*
- *Gender (1=Male / 0=Female)=gender*
- *BMI at visit 1 (continuous)= BMI_v1*
- *Had any PDPE during DBP (1=Yes / 0=No)= hadpe_DBP*
- *Pseudomonas aeruginosa (mucoid) infection during DBP (1=Yes / 0=No)=pa*
- *Burkholderia cepacia infection during DBP (1=Yes / 0=No)=bcc*
- *Staphylococcus aureus infection during DBP (1=Yes / 0=No)=staph*
- *Pain* reported during DBP (1=Yes / 0=No)=pain*
- *Pharyngolaryngeal pain reported during DBP (1=Yes / 0=No)=phary*
- *Respiratory symptoms (1=Improved / 0=Not improved)=resp4*
- *Vitality (1=Improved / 0=Not improved)=vit*
- *Physical symptoms (1=Improved / 0=Not improved)=phys*
- *Responder (1=Responder/0=Non-responder)= resp*
- *Unsuitable for rhDNase use (1=Unsuitable/0=Suitable/Other)= unsuit*
- *RhDNAse user (2=User / 1=Non-user)= RHDNASE*

** Pain is defined as follows: if the preferred term of the reported adverse event contains the word "pain" or headache.*

To be noted that for the respiratory symptoms, vitality and the physical symptoms variables the minimal clinical important difference (MCID) was used to determine the categories as follows: the change from baseline at visit V4 score is compared to the MCID values. The following MCID values were used:

- *Respiratory symptoms: MCID=4 (based on the Quitner paper)*
- *Vitality: MCID=8.6*
- *Physical symptoms: MCID=8.4*

3. METHOD

A univariate analysis was performed using PROC TTEST (for categorical variables) and PROC CORR (for continuous variables) in SAS.

4. RESULTS

4.1 Univariate Analysis

The analysis was performed on the adult intent-to-treat patient population (ITT) on the pooled 301 and 302 study populations. There are 265 patients in this subset.

The following variables were found as significant at the 0.05 level:

Quantitative:

- *FEV1 percentage predicted at visit 4 (continuous)= fev1p_locf*
- *FEV1 percentage predicted at visit 1 (continuous)= fev1p_imp1*

Qualitative:

- *RhDNAse user (2=User / 1=Non-user)= RHDNASE*

The Pearson correlation coefficients, the p-value and the number of observations are presented in Table 1 for the continuous variables.

Table 48. Pearson correlation coefficients, the p-value and the number of observations – Adults rhDNase non-users unsuitable to take rhDNase.

	fev1p_locf	AGE	bmi_v1	fev1p_imp1
Total_costs	-0.18485 0.0037 245	-0.04680 0.4481 265	-0.11950 0.0520 265	-0.19040 0.0018 265

The results of the t-test for the categorical variables are presented in Table 2.

Table 49. FEV1 % predicted at visit 4 by different categorical variables – Adults rhDNase non-users unsuitable to take rhDNase.

Variable	N	Mean[SD]	95% CI	p-value (t-test)	p-value (Wilcoxon)
Treatment group				0.7431	0.1314
Control	99	4664.4 [5491.9]	[3569.1; 5759.8]		
Mannitol	166	4390.7 [7135.6]	[3297.2; 5484.2]		
Gender				0.3435	0.0346
Female	101	4980.4 [6537.6]	[3689.8; 6271.0]		
Male	164	4192.8 [6576.1]	[3178.8; 5206.7]		
PA infection during DBP				0.3271	0.0738
No	116	4044.5 [6195.0]	[2905.1; 5183.8]		
Yes	149	4842.1 [6831.3]	[3736.2; 5948.0]		
BCC infection during DBP				0.5201	0.1175
No	241	4410.9 [6678.2]	[3563.5; 5258.4]		
Yes	24	5316.4 [5275.6]	[3088.7; 7544.1]		
Staphylococcus infection during DBP				0.2144	0.0261
No	146	4945.3 [6852.2]	[3824.5; 6066.1]		
Yes	119	3937.9 [6166.5]	[2818.5; 5057.4]		
Pain during DBP				0.2483	0.0360
No	176	4161.6 [6500.0]	[3194.6; 5128.6]		
Yes	89	5148.2 [6666.0]	[3744.0; 6552.4]		
Pharyngolaryngeal pain				0.5909	0.6989
No	246	4553.3 [6690.8]	[3713.1; 5393.5]		
Yes	19	3711.4 [4603.4]	[1492.7; 5930.2]		
Respiratory Symptoms				0.5075	0.1590
Not improved	133	4949.3 [6271.9]	[3873.5; 6025.1]		
Improved	94	4373.8 [6656.2]	[3010.5; 5737.1]		
Vitality				0.6405	0.2724

Variable	N	Mean[SD]	95% CI	p-value (t-test)	p-value (Wilcoxon)
Not improved	181	4610.3 [5734.6]	[3769.2; 5451.4]		
Improved	46	5107.3 [8695.6]	[2525.0; 7689.6]		
Physical symptoms				0.6370	0.7814
Not improved	189	4620.5 [5889.9]	[3775.3; 5465.6]		
Improved	38	5161.2 [8699.1]	[2301.9; 8020.5]		
Responder				0.5883	0.4181
Non-responder	146	4295.5 [5895.8]	[3331.1; 5259.9]		
Responder	119	4735.2 [7311.8]	[3407.9; 6062.5]		
Suitability for rhDNase use				0.7027	0.3450
Suitable	214	4568.2 [6265.7]	[3724.0; 5412.5]		
Unsuitable	51	4177.0 [7737.2]	[2000.9; 6353.2]		
rhDNase use				0.0009	<.0001
Non-User	106	2870.6 [5716.8]	[1769.6; 3971.6]		
User	159	5574.5 [6873.7]	[4497.8; 6651.2]		