in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Single Technology Appraisal:

Mannitol dry powder for inhalation for the treatment of cystic fibrosis

Addendum to Evidence Review Group's Report following Pharmaxis' new evidence submission of 3rd July 2012

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University

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1. Introduction

The Evidence Review Group (ERG) was requested by NICE to provide commentary and validity checks on the additional evidence submitted by the manufacturer.[1] It should be recognised that the work undertaken by the ERG does not constitute a full critique of the manufacturer's new evidence and does not accord with the procedures and templates applied to the original submission due to the limited time available to review the additional submission. However, a number of detailed checks were undertaken to ensure the validity of the manufacturer's revised analyses based on the new evidence provided by the manufacturer as part of its response to the ACD.

2. Clinical effectiveness

Changes from original submission

In terms of clinical effectiveness data, the new evidence provided no new data. Instead the manufacturer's new evidence included alternative analyses of data from the two most relevant trials in their original submission.

ERG commentary

The same critique applies as to the original submission. In summary:

1. Population: The new evidence uses data from the pooled adult rhDNase non-users population in both relevant trials, i.e. 49 in the mannitol arm and 85 controls (total: N=134).

As can be seen from table 11 (page 38) of the original ERG report, these numbers can be calculated by subtracting the number of adult rhDNase users from the number of adults. However, the relevant population according to the NICE scope is 'Adults with cystic fibrosis who are ineligible, intolerant, or inadequately responsive to rhDNase'. In other words, 45 in the mannitol arm and 20 controls (total: N=65). This is less than 50% of the trial participants included in the manufacturer's analyses. It is unclear how different the results would be using data from the population as defined in the NICE scope.

Table 11 (original ERG report): Numbers of patients by intervention and subgroup in study 301 and 302

Study:	Study 301			Study 302		
Intervention:	Mannitol	Control	Total	Mannitol	Control	Total
Total	177	118	295	184	121	305
Adults	114	76	190	93	58	151
RhDNase users	96	67	163	137	92	229
Adult rhDNase users	58	44	102	64	41	105
Adults ineligible, etc.*	30	13	43	15	7	22

* Adults with cystic fibrosis who are ineligible, intolerant, or inadequately responsive to rhDNase

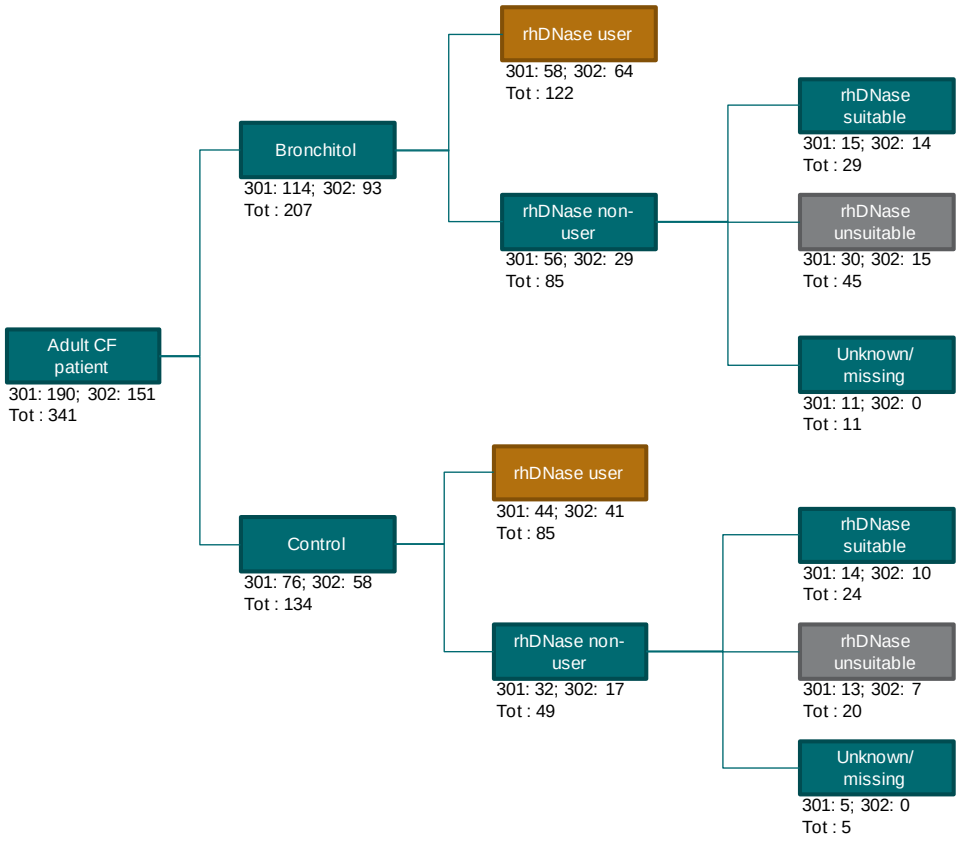
2. Outcomes: Only data for FEV1 % predicted and exacerbations are reported. No other outcomes mentioned in the NICE scope are reported. Data on mortality are not assessed in any of the studies included in the new evidence; and data on respiratory symptoms, exercise tolerance, adverse events and health-related quality of life are not reported for the relevant subgroups in this appraisal.

3. Comparators. There is insufficient data for a reliable comparison between mannitol and hypertonic saline.

Regarding the population, the following information is available from the manufacturer's response to the clarification letter.[2]

Figure 1 on page 2 of the manufacturer's response to the request for clarification from the ERG provides the proportion of adults ineligible, intolerant or inadequately responsive to rhDNase in the pivotal studies.

Figure 1 (from manufacturer's response to the clarification letter). Proportion of adults ineligible, intolerant or inadequately responsive to rhDNase in the pivotal studies



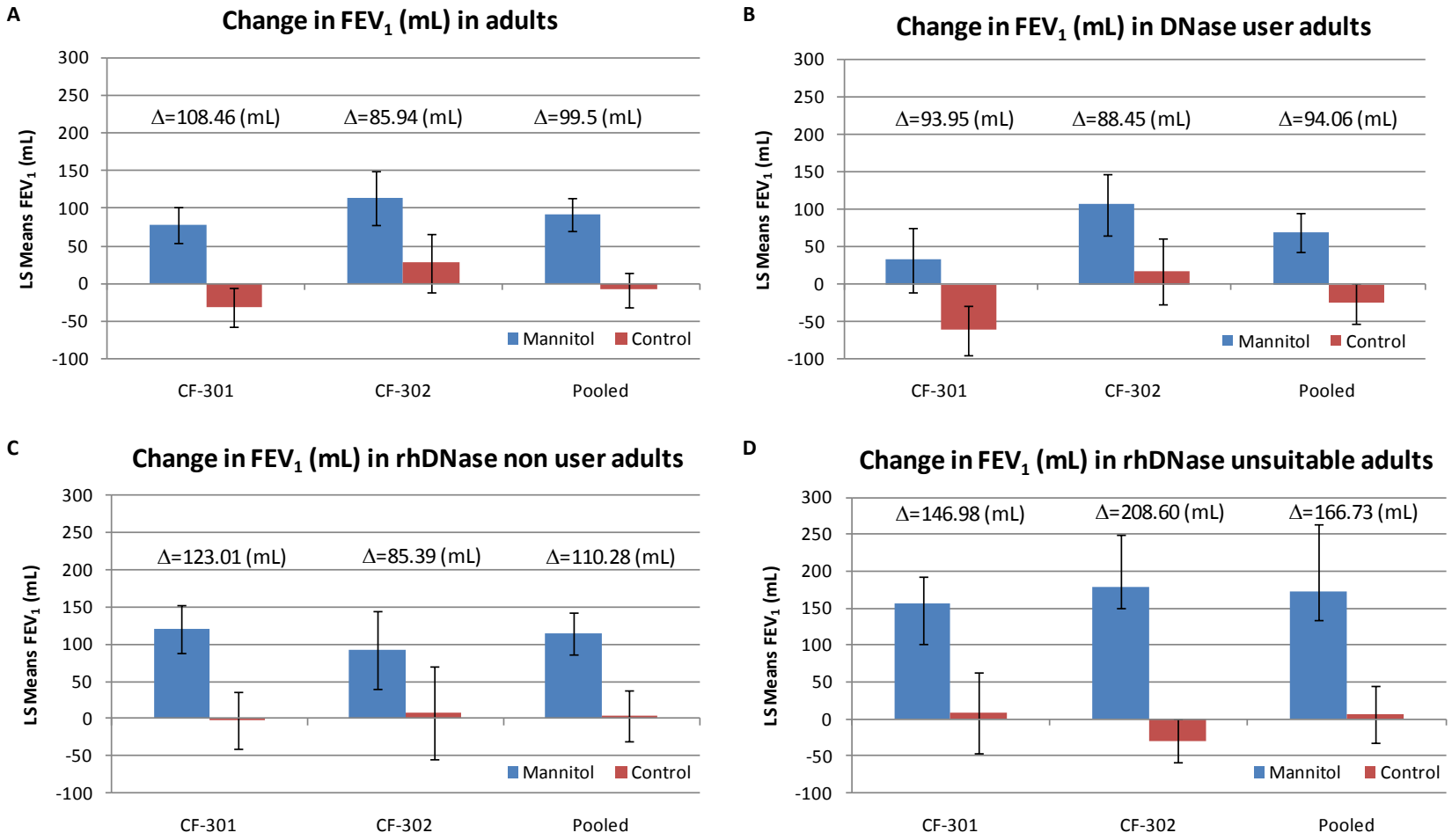
Note: rhDNase unsuitable refers to patients that are ineligible, intolerant or inadequately responsive to rhDNase.

Figure 2 on page 4 of the manufacturer's response to the clarification letter provides data for changes in FEV1 for different subgroups, and tables 1 and 2 on page 6 provide data for the incidence and rate of exacerbations in the different subgroups.

Looking at the data in Figure 2, it seems that the difference between mannitol and control in change in FEV1 is larger in the unsuitable population (Δ = 166.73 mL) than in the non-user population (Δ = 110.28 mL). Looking at the data in Table 2 of the manufacturer's response to the clarification letter, it seems that the difference between mannitol and control in exacerbation rate is similar.

The main problem with using data from the unsuitable population is that the numbers of patients included in the analyses is very low (N=65); therefore, the results are very uncertain.

Figure 2 (from manufacturer's response to the clarification letter). 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 mannitol and control

Table 1. (from manufacturer's response to the clarification letter). 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 (from manufacturer's response to the clarification letter). 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.

3. Cost-effectiveness

As part of the manufacturers' response to the ACD, the original cost-utility analysis (CUA) provided as part of the manufacturer's submission has been updated to reflect the comments received by the ERG and the Committee. The manufacturer presents an economic evaluation for the subgroup of patients receiving Best Supportive Care (BSC) without add-on rhDNase (non-users).

In addition the manufacturer has consulted with CF clinicians about concerns raised by NICE that the stopping rule proposed was unlikely to be adhered to. As a result a 0% improvement in FEV1% predicted at 6 weeks is now proposed as a stopping rule in order to ease clinical implementation.

No modifications to the core model structure have been made to this revised model. The model that was developed for the current economic evaluation is a patient-level simulation Markov model which means that the progression of each individual patient is modelled, rather than the progression of a whole patient cohort at once.

Changes from original submission

Below two lists of the parameters and characteristics of the model that have been changed from the original model are provided. The first list contains (potentially) important changes that will be discussed in the ERG commentary, the second list presents minor modifications that have little to no impact on the point estimate of the ICER which will therefore not be further discussed.

The following important changes were made to the original model:

1. The cost-effectiveness of Mannitol has been analysed in adult CF patients, when added as a treatment for patients currently receiving BSC without rhDNase (non-users). All relevant clinical and effectiveness input parameters have been adapted to the new target population;
2. The analysis incorporates a new responder definition (0% improvement in FEV1 % predicted at 6 weeks);
3. The model framework has been modified to reflect treatment-independent costs and utilities for respiratory symptom improvement, when valuing health states as suggested by the ERG;
4. The outcomes at 26 weeks were carried forward for the next 4 cycles in the model (48 weeks) unless the patient died;
5. Mannitol responders are allowed to discontinue treatment. All drop-outs are switched to best supportive care;
6. The annual exacerbation rate for patients in the control group has been recalculated according to the proposed ERG methodology;

Additionally, the following minor changes were made. Note that under a) now the costs of the initial dose assessment (BIDA) have been included (£8.27) while in the original submission these costs were set to 0.

a) Costs of mannitol have also been updated to £16.55 and the cost for the mannitol initiation dose assessment (BIDA) test is now considered on an ITT basis;
b) The hazard ratio for FEV_1 % predicted is now based on a Cox model with only FEV_1 % predicted as explanatory variable (original model HR 0.957, modified model HR 0.952);
c) Patients with missing data from the Quality of Life instrument (CFQ-R) were considered as "not improved in respiratory symptoms;
d) The probability of dying for patients with Burkholderia cepacia (Bcc) infection or experiencing an exacerbation was adjusted by the relative risk being applied to the probability of mortality instead of a mortality rate;
e) Parameters of the beta distribution for a utility decrement due to exacerbation have been adjusted;
f) Duration of utility decrement has been increased based on recommendations provided by the ERG and a new distribution is defined to reflect second order uncertainty;
g) Parameters of the gamma distributions of the cost estimates have been adjusted to reflect second order uncertainty.

Revised input data

We discuss here for each item on the first list which changes were made:

Ad 1) all input parameters that are population dependent were re-estimated. We refer to section 2.3.3, 2.4 and 2.5 of the manufacturer's response to the ACD for tables indicating which parameters were modified. To summarize for groups of parameters:

- Characteristics of the patient population were re-estimated from the trial data to reflect the sub-group of rhDNase non-users (see Table 2 new evidence);
- The treatment effect on FEV1 % predicted at week 26 was re-estimated using OLS regression analysis using the same methodology as in the original manufacturer's submission. Note that not only is the regression analysis run for a new sub-group, also the definition of the covariate 'responder' was changed (see Table 5 new evidence);
- The response rate was now calculated using trial data for the rhDNase non-users (note that also the definition of responder has been changed, see ad 2);
- The relative risk of an exacerbation for mannitol users compared to control was re-estimated using the trial data from the rhDNase non-users while applying the new definition of responder (see Table 6 new evidence). The methodology used to estimate the relative risk is the same as in the original manufacturer's submission.
- The transition probabilities for improved respiratory symptoms after 3 and 6 months were re-estimated using the trial data from the rhDNase non-users. The methodology

used to estimate these probabilities is the same as in the original manufacturer's submission (see Table 9 new evidence).

- The base line utility and the utility increments/decrements for patients with and without improvement in respiratory symptoms were re-estimated using the trial data from the rhDNase non-users. The methodology used to estimate these is the same as in the original manufacturer's submission (see Table 17 new evidence).
- Costs for patients with and without improvement in respiratory symptoms were re-estimated using the trial data from the rhDNase non-users. The methodology used to estimate these is the same as in the original manufacturer's submission (see Table 18 new evidence).

Ad 2) As a result of a new responder definition, the response probability increased in both groups. According to the previous definition responders are patients achieving ≥5% relative improvement in FEV_1 or an absolute improvement of ≥100 ml in FEV_1 measured at the 6 week-visit, whereas with the new definition responders are all patients with a relative increase of at least 0% in the FEV_1 predicted at week 6 from baseline (i.e. the FEV1 % predicted should not have declined at week 6). For non-users, with the previous definition, the mannitol response rate was 55% versus 37% for control. With the new definition these percentages are 69% and 55%, respectively (see Table 7 new evidence).

Also, as a result of the new response definition, various other input values change, see ad 1).

Ad 3) In the ERG base case presented in the original ERG report, we already included health state specific costs and utilities, rather than treatment specific. In the manufacturer's response to the clarification letter the change in utility for patients with improvement in respiratory symptoms was 0.015 versus -0.031 for patients with no improvement. This was based on the whole trial population. In the new analyses provided with the ACD response the changes in utility are 0.025 and 0.001, respectively. The fact that these are other values suggests that they are specific for the population of non-users, though this is not explicitly stated in the report.

For the costs, the ERG base case assumed for the unsuitable, ineligible and intolerant rhDNase non user subgroup population costs of £3,885 for patients with improvement in respiratory symptoms versus £4,385 for patients without improvement. In the population of non-users in the manufacturer's new analyses, these cost estimates are £2,307 and £3,255, respectively. Note that the cost estimates are based on patient level resource use data collected during the trials, and that only aggregate data was presented in the original manufacturer's submission.

Ad 4) The extension trials of CF301 and CF302 (pg. 91 of MS) demonstrated that the treatment benefit of mannitol is maintained for up to the 78 weeks. Thus, the new analyses provided with the ACD response assumes that the % predicted FEV1 at 26 weeks is maintained during 4 cycles (i.e. until week 74) after which the % predicted FEV1 starts to

decline according to the natural decline. In the original manufacturer's submission, it was assumed that the natural decline would start at week 26.

Ad 5) In the original manufacturers submission, patients could only switch to control if the patient is a non-responder at week 6. In the new analyses provided with the ACD it is assumed that also mannitol responders may discontinue treatment due to for example poor compliance. Just as the non-responders, these later drop-outs are assumed to switch to control. Based on the percentage of patients withdrawing from the double blind and the open label phases of the DPM-CF-301 and DPM-CF-302 studies an annual drop-out rate was estimated of 0.39.

Ad 6) In the original ERG report we stated that the ERG is uncertain about the way the exacerbation rate (0.7) was calculated based on Australian data from Biogrid and we suggested an alternative approach to the calculation (see page 68 of original ERG report), leading to an higher baseline exacerbation rate of 1.01. This alternative approach is now implemented in the modified model.

Results of the manufacturer's new analyses for the rhDNase non-user subgroup

The base case results are presented below.

Table 3 Base-case results non-users

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Control	171,619	11.27	9.96				
Mannitol	182,456	11.84	10.50	10,837	0.57	0.54	19,993

Univariate sensitivity analysis
Extensive univariate sensitivity analysis was performed on all input parameters. Most changes to input had minimal effect on the outcome.

As in the original submission, the model was most sensitive to parameters related to exacerbations. The most influential parameter is the relative risk of a pulmonary exacerbation for patients responding to mannitol treatment. This is due to the high uncertainty around this parameter (mean=0.40 95% CI= [0.17; 0.91], for mean see Table 6 new evidence, CI see page 28 new evidence). Smaller, but noticeable, effects were seen when the baseline exacerbation rate, the value of the utility decrement for exacerbation, and the cost to treat a pulmonary exacerbation were varied.

When looking at the parameters related to lung functioning, the effect of mannitol on the change in FEV_1 % predicted at 26 weeks was the most influential parameter in the model.

Again, this is due to the high uncertainty around this parameter (mean=1.121, 95% CI= [-1.39; 3.63], for mean see Table 5 new evidence, CI see page 28 new evidence). Also the patient's FEV_1 % predicted at baseline had a significant impact on the model, the ICER being lowest in patients with lower FEV_1 % predicted.

Finally, the background cost of CF for patients without improvement of respiratory symptoms had a large impact on the ICER.

Probabilistic sensitivity analysis

Figures 3 and 4 present the outcomes of the PSA plotted on the CE-plane and the acceptability curve, respectively. The probability of the ICER being below a WTP threshold of £30,000 was 82.2%. At a WTP threshold of £20,000 this probability was 46.5%.

Figure 3 ICER scatter plot

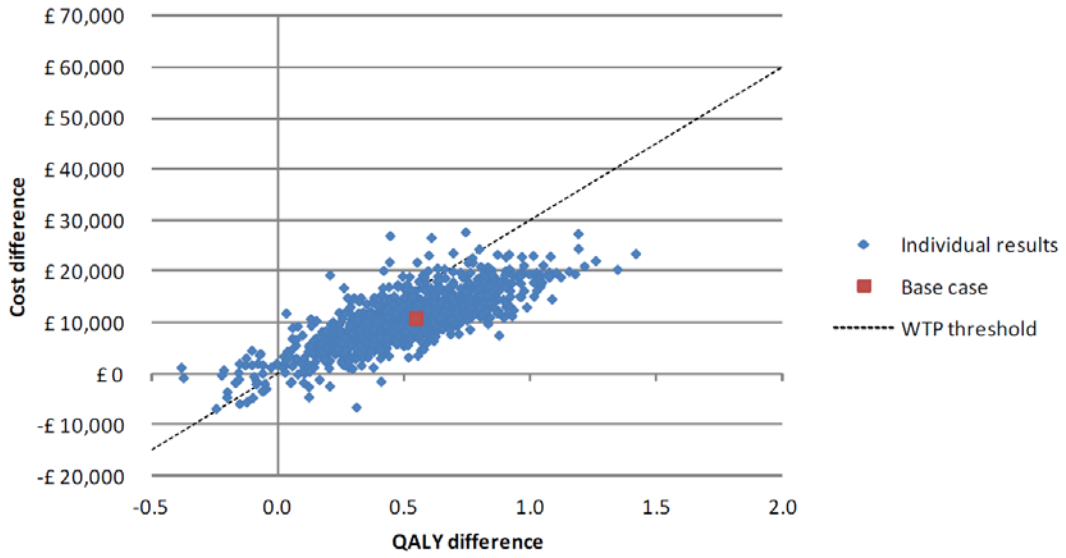
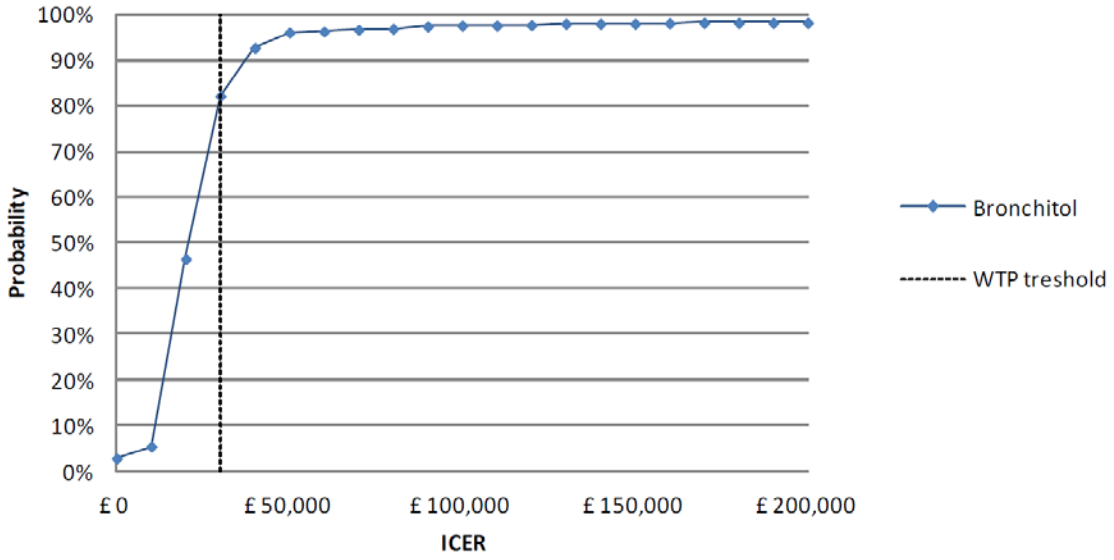


Figure 4 Cost-effectiveness acceptability curve



Scenario analysis

Table 4 presents the results for 3 scenarios relating to 2 changes made in the original model, i.e. duration of stable % predicted FEV1 for patients receiving mannitol and the inclusion of drop-out in the mannitol group. The new base case analysis assumes that the % predicted FEV1 at 26 weeks is maintained during 4 cycles (i.e. until week 74) after which the % predicted FEV1 starts to decline according to the natural decline. The new base case also assumed an annual drop-out rate of 0.39. The first ICER presented in table 4 shows that both the incremental costs and the incremental QALYs increase, resulting in a decreasing ICER when both changes are not implemented.

The second ICER is the situation where no drop-out is included, whilst the % predicted FEV1 at 26 weeks is carries forward for 48 weeks as in the base case analysis. This shows that the impact of including the drop-out is more important than that of the number of cycles the % predicted FEV1 at 26 weeks is maintained.

Table 4 Results scenario analysis for maintained treatment benefit and drop-out rate

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (QALYs)
% predicted FEV_1 at 26 weeks not carried forward and no drop-out included							
Control	171,619	11.27	9.96				
Mannitol	193,634	12.55	11.23	22,014	1.28	1.27	17,312
% predicted FEV_1 at 26 weeks carried forward for 4 cycles and no drop-out included							
Control	171,619	11.27	9.96				
Mannitol	194,637	12.62	11.29	23,018	1.35	1.33	17,274
% predicted FEV_1 at 26 weeks carried forward for 8 cycles and drop-out							
Control	171,619	11.27	9.96				
Mannitol	182,981	11.87	10.53	11,362	0.60	0.57	19,844

Table 5 presents the results when the same response definition is used as in the original submission, i.e. responders are defined as patients achieving ≥5% relative improvement in FEV_1 or an absolute improvement of ≥100 ml in FEV_1 measured at the 6 week-visit. This

analysis clearly shows that the change in response definition has little impact on the results (base case ICER £19,993)

Table 5 Results scenario analysis using a modified responder definition

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (QALYs)
Control	170,658	11.21	9.91				
Mannitol	180,926	11.77	10.44	10,268	0.56	0.53	19,550

Finally the impact of a shorter time horizon as a proxy for a shorter duration of effectiveness of mannitol (i.e. shorter than life time) was assessed. In essence, the assumption is made that after 5/10/50 years mannitol is no longer effective, such that the patients FEV1 drops to that of the control group, leading to discontinuation of mannitol. Going from a life time time horizon to 10 years increase the ICER by 25%, while a 5 year time horizon yields an ICER more than 100% higher. This result is explained by the fact that the incremental effects are mostly due to increased life expectancy, and with a shorter time horizon this increase cannot materialize.

Table 6 Results varying time horizon

Variable	Mannitol cost (£)	Mannitol QALYs	Control cost (£)	Control QALYs	Incremental Cost (£)	Incremental QALY	ICER (£)
Time horizon 5 years	64,285	3.86	61,929	3.81	2,357	0.05	45,329
Time horizon 10 years	109,879	6.47	106,311	6.33	3,568	0.14	25,151
Time horizon 50 years	182,019	10.48	171,278	9.94	10,741	0.54	20,018

Additionally, the manufacturer also explored different values of the base line risk of exacerbation. In the base case, the annual rate was 1.01 (as opposed to 0.7 in the original submission). In the scenario analyses, rates of 1.5, 2 and 3 were used, leading to ICERs between £18,000 and £19,000.

ERG commentary

The structure of the model submitted by the manufacturer was identical to that in the original submission. However, the manufacturer made various changes to the input values, some of them related to a change in patient population: in the current submission the population is defined as BSC without rhDNase. Note that in the original ERG report, the ERG explored the population of patients with BSC unsuitable for rhDNase (i.e. ineligible, intolerant or inadequately responsive to rhDNase), which is a subgroup of the current population (see also figure 1).

The ERG checked whether all changes had been implemented in the model correctly, no errors were found.

Several of the major changes made to the model were investigated in scenario analyses. It is interesting to note that most of the changes do not have a large impact on the ICER: allowing drop-outs, definition of response, and extrapolation of the FEV1 at 26 weeks to 74 weeks all have a limited impact on the ICER.

However, in the original ERG report, we presented an ERG base case for the rhDNase unsuitable population with an ICER of £30,000. The manufacturer's new model ICER, for the non-users, is £20,000. This seems a large difference as the unsuitable population is a subset of the non-users population. Also, as indicated at page 4 of this document, the difference between mannitol and control in change in FEV1 is larger in the unsuitable non-user population (Δ = 166.73 mL) than in the whole non-user population (Δ = 110.28 mL). This suggests that mannitol is more effective in the unsuitable population than in the whole non-user population, which would suggest an increase in the ICER if the whole non-user population is considered rather than only the unsuitable non-users.

We have therefore explored which changes in the manufacturer's new model are most important in counteracting this potential increase in ICER. This procedure can be done in two ways, either by using the original model and adding the changes one by one (forward procedure), or by starting with the modified model and undoing changes one at a time (backward procedure). Since the original model was based on the unsuitable population the number of changes that need to be made is much smaller for the backward procedure, so we have explored changes stepwise, taking the manufacturer's new model and changing back various parameters to their original values.

From this (see Table 7), it is clear that the most influential changes to the model are the exacerbation rate, which is now correctly estimated, the inclusion of drop outs in the mannitol group and the different estimate for costs of best supportive care. The importance of changing the costs is due to the fact that the difference in costs between patients with and without improvement is smaller in the original model (unsuitable non-users, Δ=£500) than in the revised model (all non-users, Δ=£948). It is unclear why the cost difference between improved and not improved patients is larger in the whole non-user population than in the RhDNase unsuitable non-user population.

Table 7 Results step wise changing back various parameters

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (QALYs)
Annual exacerbation rate control group 0.7							
Control	148,260	11.81	10.49				
Mannitol	159,572	12.36	11.01	11313	0.55	0.52	21,772
Idem and no drop-out included							
Control	148,260	11.81	10.49				
Mannitol	179,603	12.95	11.62	31,343	1.14	1. 13	27,854
Idem and 'unsuitable' costs per health state (higher costs, see page 9)							
Control	176,479	11.81	10.49				
Mannitol	212,107	12.95	11.62	35,628	1.14	1. 13	31,662

Based on the findings in Table 7, we conclude that it is plausible that, despite changing to a subgroup with a smaller increase in FEV1 % predicted, the ICER has changed from £30,000 to £20,000.

Regarding the changes to the costs of BSC for patient with and without improved respiratory symptoms, we observe that the costs for all non-users are lower than for the unsuitable non-users implying very low costs for suitable non-users. From table 49 in the response to the clarification letter we derived that, on average, the 6-month cost observed in the rhDNase non-user group is £2870. For the group unsuitable for rhDNase this estimate is £4177 and for the suitable group this would be £1659.
We observe something similar for the utilities; the unsuitable non-users patients without improved respiratory symptoms had a utility decrement whereas for all non-users, these patients without improvement have a very small increase in utility, which implies a larger increase in utility in the suitable non-users.
This clearly indicates that the non-users group of patients is not homogeneous, i.e. the unsuitable group has lower utility, higher costs and larger improvement in FEV1 % predicted than the suitable group. This suggests that the cost-effectiveness ratio may expected to be lower in the subgroup of patients who are unsuitable, ineligible and intolerant of rhDNase than in the suitable sub-group and hence also lower than in the whole non-user population.

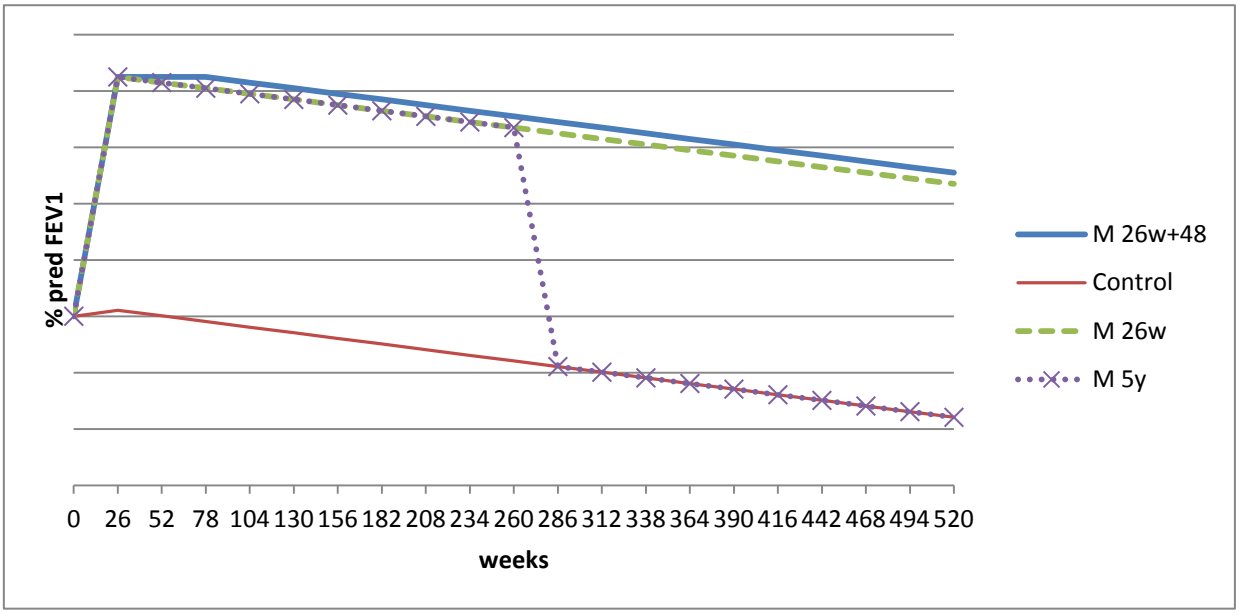
Regarding the cost estimates used in the model, we indicated in the original ERG report that since no counts of resource use were presented, nor a list of unit costs used, it was difficult to check the validity of the cost estimates. This is true for the current estimates as well. Though no details are given, it appears that resource use by all patients, located in 11 different countries, is multiplied with UK unit costs. Such procedure is common, but only valid if the management of the disease in the UK is approximately the same as in the various other countries included. Neither the original manufacturer's submission nor the new evidence contains such assessment.

In the report of the revised model, the manufacturer assumes that the % predicted FEV1 at 26 weeks is maintained during 4 cycles (i.e. until week 74) after which the % predicted FEV1 starts to decline according to the natural decline. In the original submission, it was assumed that the natural decline would start at week 26. In addition, in the scenario analyses, a scenario is explored in which the time horizon is set to e.g. 5 years, as a proxy for a shorter duration of effectiveness of mannitol.

To illustrate how these different options for long term effectiveness influence FEV1 % predicted, we produced the following graph (figure 5). The thin line represents the natural decline in the control group. The solid thick line shows the new base case, where the FEV1 % predicted at 26 weeks is maintained until week 74, after which it starts to decline at the same rate is in the control group (i.e. the lines are parallel). The dashed line represents the assumption in the original submission, that after 26 weeks the FEV1 % predicted declines as in the control group. Note that in this graph, the difference between the 2 scenarios is minimal. Finally the dashed line with X markers presents the scenario where mannitol is assumed to stay effective for 5 years, after which a rapid decline to the control curve occurs. This graph illustrates why the latter scenario (ICER £45,000) has a large impact on the ICER, whereas the change from starting the decline at 74 weeks (base case ICER £20,000) to starting the decline at 26 weeks (ICER £20,500) has a relatively small impact on the ICER.

While it is always difficult to make assumption about long tern effectiveness when no data exists, some suggestion of what might be a reasonable assumption is given by the study by Konstan & Ratjen [3]. In this study, they have assessed the long term effectiveness of treatment with rhDNase, and they conclude that the annual decline in patients receiving rhDNase is approximately 66% of the natural decline without rhDNase. This suggests that the current assumption for mannitol. i.e. a decline of 100% of the natural decline, is not unreasonable and may even be regarded as conservative.

Figure 5 Various scenarios long term extrapolation effectiveness mannitol



Regarding the drop-out rate applied in the modified model after 6 weeks, the annual rate of 0.39 was calculated based on observed patient withdrawal during the double blind and open label phases of the clinical studies, up to 78 weeks. This rate appears high, as it means that a patient starting treatment with mannitol would have a 32% probability of dropping out in the first year, assuming the patient was a responder at 6 weeks. Ultimately, whether this assumption is reasonable or not should be checked with clinical experts.

All in all, we conclude that the changes made to the original model have been implemented correctly. Some of the changes were in line with suggestions made in the ERG report. Other changes, such as the definition of responder and the inclusion of drop-out appear reasonable to the ERG. However, it is important to realize that in this document we have only discussed the changes made by the manufacturer. This means that any comments that the committee had on the original submission that have not led to changes in the model still apply.

4. References

[1] Quintiles (on behalf of Pharmaxis). *Mannitol (Bronchitol®) dry powder for inhalation for the treatment of adult patients with cystic fibrosis [ID85]. A report of the Revised Cost-Utility Analysis to support the manufacturer's responses to the preliminary ACD. rhDNase non-users.*, 3 July 2012

[2] Pharmaxis. Mannitol dry powder for inhalation for the treatment of cystic fibrosis – response to request for clarification from the ERG. Burnham, UK: Pharmaxis, 2011: 61p.

[3] Konstan MW, Ratjen F. Effect of dornase alfa on inflammation and lung function: Potential role in the early treatment of cystic fibrosis. J Cyst Fibros. 2012 Mar;11(2):78-83.