Committee papers Mannitol Sept meeting

In addition to the comments on the ACD the manufacturer sent a number of other files including new analyses (as shown below). These files included a large number of pdf versions of publications, which we cannot include in Committee papers for copyright reasons. Also included were confidential third party documents relating to the regulatory process.
The EPAR is now publicly available under Assessment History at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001252/human_med_001475.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124)

The SPC is publicly available at http://www.medicines.org.uk/EMC/searchresults.aspx?term=Pharmaxis+Pharmaceuticals+Ltd&searchtype=QuickSearch

For the decision about which of the additional material can be accepted at this stage in the appraisal, the criteria set out in section 3.5.34 of the STA process guide were followed, and an independent critique of the first additional subgroup analysis (files 5 and 6) and the survey (file 24) were requested to be available to the Committee.

files received	included in Committee papers
1. Pharmaxis response to ACD	yes
2. Pharmaxis confidentiality disclosure	No (as in standard procedure)
3. Clinical trial protocol for DPM-CF-301	yes
4. Clinical trial protocol for DPM-CF-302	yes
5. Cost utility analysis for rhDNase non-users	yes
6. Model for cost utility analysis for rhDNase non-users	No, but will be critiqued by ERG
7. Cost utility analysis for FEV1% predicted rapid decline group	No
8. Model for cost utility analysis for FEV1% predicted rapid decline group	No
9. Adis drug profile on mannitol	No
10. Aitken et al paper on DPM-CF-302 published in AJRCCM	No
11. Aitken et al poster on DPM-CF-302 open label phase data	No
12. 2009 CF Trust annual report from Australia	No
13. Bilton et al poster on DPM-CF-301 open label phase data	No
14.Bilton et al paper on DPM-CF-301 from European Respiratory Journal	No
15. CHMP guidance on CF guideline development	No
16. Consensus letter to CHMP on original CHMP negative opinion on mannitol	No
17. Dentice et al (including Elkins) abstract on a review of pulmonary exacerbation definitions – not sure where published	No

18.Goss and Burns paper in Thorax on pathophysiology of pulmonary exacerbations	No
19. Minutes from SAG meeting at EMA on mannitol October 2011	No
20. Schluchter et al paper in AJRCCM on FEV1% pred as a predictor of longitudinal outcomes	No
21. Schluchter et al supplement to paper in AJRCCM on FEV1% pred as a predictor of longitudinal outcomes	No
22. Taylor-Robinson et al study on longitudinal FEV1% predicted decline supplementary materials	No
23. 22. Taylor-Robinson et al paper in Thorax on longitudinal FEV1% predicted decline	No
24. UK Treatment Pathway survey (small web based study that Pharmaxis did on their own accord to let us know that HS and rhDNase would not be replaced by mannitol, and to make the case that mannitol would be unlikely to be used as a first line agent and that it would help in people with uncontrolled CF.	Yes, will be critiqued by the ERG

EXECUTIVE SUMMARY

We thank the Committee for an opportunity to comment on the preliminary Appraisal Consultation Document (ACD) of inhaled mannitol (Bronchitol®) in adult patients with cystic fibrosis (CF) [ID85]. In providing the following response, the manufacturer has sought to address as many of the Committee's and Evidence Review Groups (ERG) concerns as possible.

A number of the concerns highlighted in the ACD have arisen as a result of the extended regulatory process to which Bronchitol has been subjected. Since the original submission to NICE (February 2011) the licensed indication has changed, as has the patient group for which the product is indicated in. In turn, this has had a substantial impact to the data and proposition with regards to the intended population.

The manufacturer has taken on board the comments from committee and the ERG, and has also sought further guidance and clarification from the CF community. As a result, the manufacturer has undertaken a full review of the cost-utility analysis (CUA) presented to NICE. In providing this response, additional information and data analysis has been identified to improve the evidence-base and assist with highlighted areas of uncertainty. The proposal within acknowledges the comments received from the Committee and now more accurately reflects the needs of the CF community. We believe that this revised proposal would enable NICE to recommend access to a new treatment option in England and Wales for those CF patients that have the most unmet medical need and where Bronchitol delivers a significant step change in both efficacy and ease of use.

Revised proposition, cost-utility analysis and budget impact of Bronchitol to England and Wales

To reflect the comments received by NICE and the needs of the CF community, the manufacturer has identified two CF patient populations who have the most unmet medical need and in which inhaled mannitol provides a significant clinical benefit.

- **Patients receiving Best Supportive Care (BSC) without add-on rhDNase.**
- **Patients receiving BSC (+/- rhDNase) experiencing a greater than 2% decline in FEV1 percent predicted per year.**

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.

To assess the clinical and economic impact of these propositions, the CUA has been revised as follows:

- To reflect the two base cases from the revised proposition (above) and the change in the stopping rule.
- The CUA model was updated in line with comments received from the ERG and NICE. (Details of the revision are provided below and within the analysis reports attached).
- To address concerns raised by the ERG and NICE, additional sensitivity and scenarios analysis have been modelled to examine:
    - the impact of key clinical and economic influences on the model,
    - the duration of treatment effect
    - drop-out rates

Base case ICERs in the two sub-populations identified above were:

- **£19,993 /QALY in patients receiving BSC without add-on rhDNase**
- **£36,214/QALY in patients experiencing a greater than 2% decline in FEV1% predicted per year.**

In probabilistic sensitivity analysis (PSA), for patients receiving BSC without add-on rhDNase, the probability of the ICER being below a willingness to pay (WTP) threshold of £30,000 was 82.2% and at a WTP of £20,000 was 46.5%. In patients experiencing a 2% decline in FEV% predicted per year, probabilities were 20.8% and 1.2%, respectively.

The manufacturer noted NICE's concerns that Bronchitol might replace hypertonic saline (HS). The manufacturer commissioned independent market research that suggests that these concerns are unfounded (see patient pathway notes below). The manufacturer would still accept eligibility criteria in any NICE recommendation to prevent switching of patients from HS that may be otherwise well controlled should NICE deem this necessary. The manufacturer is reluctant to propose specific wording given that the use of HS at doses proven to be effective in reducing exacerbations is low, there has been no regulatory review of safety and efficacy, and no RCTs performed in patient populations with the same demographic makeup as patients found in UK CF clinics.

Finally, in considering the eligible patient population likely to receive mannitol (based on the patient treatment pathway analysis), the estimated acquisition cost for Bronchitol in year-1 would be estimated as ~ £1.2M rising to £3.3M in year-5. This represents low cost compared to other treatment in CF

Current treatments

CF is an inherited, orphan designated condition affecting an estimated 8,000 patients (estimated 4,200 adults) in the UK with a severely limited life-expectancy[1], just over half of whom are adults (defined as 18years+). Characterised by a rapid and progressive decline in lung function (FEV1) and frequent respiratory infections (exacerbations) that often lead to hospitalisation, the clinical goal for patients with CF is to prevent further loss in lung function which has been shown to correlate with increased risks of exacerbation and mortality.

Current treatment reflecting BSC in the UK is complex and is based upon the individual needs of the patient. Treatment represents a significant patient and carer burden, with daily respiratory physiotherapy, nutritional control, inhaled/oral antibiotics, bronchodilators and inhaled/oral corticosteroids. To facilitate mucocillary clearance, patients may also receive aerosolised rhDNase (Pulmozyme®), and whilst unlicensed, nebulised hypertonic saline may also be given.

Clinical study design and results

Consistent with Regulatory advice at the time, the two Bronchitol® registration trials DPM-CF- 301 (n=295) and DPM-CF- 302 (n=305) were individually powered to show (and demonstrated) statistically significant improvements in lung function for all patients (children and adults), when added to BSC. In October 2011, the EMA provided an initial indication for inhaled mannitol as a treatment in adult-only patients. This led to a reduction in the planned statistical power of the trial data, although due to the studies being of similar design and study population, the EMA accepted pooled analysis of adult patients in their evaluations (n=341). At the same time the patient population was simplified from '*...as either an add-on therapy to rhDNase or in patients intolerant to, or inadequately responsive to rhDNase' to '…add on therapy to best standard of care'*. The subgroup that is intolerant to or inadequately responsive to rhDNase was small and not predefined in both studies and was the subject of NICE concerns in the preliminary ACD. It is no longer in line with the Bronchitol approved label and has therefore been removed from the base case proposition.

In pooled analysis, when compared to Best Supportive Care (BSC with or without rhDNase), adult patients treated with Inhaled mannitol demonstrated:

- A statistically significant improvement in lung function of 99.5mL($p<0.001$) over 26 weeks whilst control patients receiving BSC experienced an average ~8mL decline in lung function over the same time period.
- This significant improvement in lung function was observed in all patients when added to BSC, regardless of patients comparatively receiving BSC, with (94.1 mL, $p<0.008$) or without (110.3 mL $p<0.005$) rhDNase.
- The improvement in lung function was sustained to at least 78 weeks in open-labelled extension studies.
- Patients switched from control to inhaled mannitol at 26 weeks, also experienced a substantial improvement in lung function. After 52 weeks of treatment, these patients had regained similar levels of lung function to those that had received inhaled mannitol throughout the trial.
- A lower exacerbation rate, with reductions in the incidence of protocol defined pulmonary exacerbations (PDPE) in the adult population of 24% (95% CI: 0.51; 1.13), when compared to BSC. Despite insufficiencies in sample sizes and event rate frequencies to satisfy statistical rigour, this consistency in trend was observed in all sub-groups
- A significant difference in PDPE rates was observed when compared to patients receiving BSC without rhDNase (Rate Reduction: mannitol: 0.38 vs. control: 0.97)
- A significant improvement in lung function and reduction in exacerbations in patients receiving BSC (+/- rhDNase) but experience the most rapid deterioration in lung function (> 2% annual decline in FEV1% predicted per year). Based on pooled data used in the CUA, change from baseline in FEV1% predicted at 26 weeks was -1.10 (95%CI: -3.72-1.52) in patients treated with BSC (+/-rhDNase) and in patients treated with inhaled mannitol: 2.71 (95% CI: 0.54-4.87), with relative exacerbation rates of 1.37 and 1.14 per year, respectively.
- An early response to treatment. After 6 weeks of treatment, an improvement in lung function was highly predicative of a continued response at 26 weeks.
- The overall safety profile of inhaled mannitol was favourable, with the most common side effects being manageable.

Bronchitol has the potential to delay the progression in lung function decline for patient with CF, and in turn reduce the associated risks of exacerbation and mortality. Bronchitol brings a clear step change in efficacy and ease of use to a patient population that has a median age of death of 29 years.

[1] **Source:** Population and Median age of death in the UK = 29 years old (min: 0- max:61), UK CF Trust Registry Report, 2010.

Manufacturer's responses to the preliminary ACD

For ease of review, in addressing areas of uncertainty highlighted by the Committee in the ACD, the manufacturer has grouped the responses by theme. In addition, the manufacturer has identified additional information and analysis to improve the evidence-base. These data have been described below:

Points of factual error: A number of factual and accuracy errors were identified in the ACD. These have been highlighted with proposed corrections stated.

Trial design, choice of primary end point and FEV_1: Provides further clarification of the trial design (with protocols attached); reasons for the choice of primary endpoint (FEV_1 percent predicted) and further details of its calculation as change over time.

Points of important clinical note: The manufacturer strongly disagrees with the comments in the ACD that Bronchitol does not represent a step change in treatment. This response highlights the medical advancement and innovation value consistent with Sir Ian Kennedys report on promoting innovation within the UK[2], that inhaled mannitol brings to patients with CF, and is further supported by a consensus statement of over 60 European CF physicians, including 12 physicians from the UK (attached).

Points of clarification on the model design: Clarification and corrections in the accuracy of the data in the manufacturers CUA, as highlighted in the preliminary ACD. In acknowledging the ERG comments on the model, a revised base case has been produced to reflect the framework and parameter modifications proposed by the ERG, with additional data derived from the actual patient-level data from the trials to improve accuracy. Full details are provided below and within the analysis report and models attached

Method and choice in extrapolating long-term outcomes: In order to extrapolate a life-time experience for patients with CF (beyond that captured within the trial period), a longitudinal, patient-level dataset was required for the CUA. In the original MS a non-UK dataset (BioGrid) was used. The use of this data was heavily criticised in the draft ACD. This section provides the rationale for using this data as the only source of longitudinal patient-level data available at the time, and provides additional research commissioned from the independently owned BioGrid dataset, to further support the UK comparability and appropriateness of using the data.

Proposed patient inclusion criteria:
Two CF patient populations are proposed.

1. **Adult CF patients not currently taking rhDNase**
   The simplification of the final EMA approved label to "...as an add on therapy to best standard of care" occurred after the manufacturer's NICE submission and reflected advice given to the CHMP by its Scientific Advisory Group that the original label referencing a subgroup that were "..intolerant to or inadequately responsive to rhDNase" was clinically inappropriate. The manufacturer now proposes for the first time a subgroup which was clearly defined in the study; those CF patients currently not taking rhDNase. This was a significant subgroup (Bronchitol: n=85; Control: n=49) and given that the majority of adult patients in the UK today have already trialled rhDNase those patients who are not now taking rhDNase by definition have a high unmet medical need. In the pooled trial data the patients not taking concurrent rhDNase had a greater treatment effect in both lung function (110.3 mL $p<0.005$) and reduction in exacerbations (Rate Reduction: mannitol:0.38 vs. control:0.97) than the ITT population.

2. **Adult CF patients with a historical lung function decline of greater than 2% per annum**
   In further evaluating sub-populations of patients by their annual rate of decline in lung function, both within the BioGrid dataset and from the two registration trials (DPM-CF-301 and DPM-CF-302), it is clear that patients presenting with the most rapid deterioration in lung function experience the most exacerbations and have the lowest life-expectancy. This is supported by a number of published studies (Liou *et al.,* 2010; Schluchter *et al.,* 2006; and Taylor-Robinson *et al.,* 2012), and represents a significant unmet need within current CF treatment. In further analysis of the pooled trial data, inhaled mannitol demonstrates a greater treatment effect in these patients; significantly reducing lung function decline and exacerbations experienced. The proposition of inhaled mannitol for patients that experience a greater than 2% decline in lung function per year is supported by the treatment effect seen in trial data and addresses a significant unmet need for CF patient*s.* Furthermore, from consulting with the CF community the manufacturer understands that similar rules are being recommended to assist as evaluation criteria for more expensive treatments for CF patients in UK clinical practice.

[2] www.nice.org.uk/aboutnice/howwework/researchanddevelopment/KennedyStudyNICEResponse.jsp

Proposed stopping rules: The manufacturer recognises that previously introduced stopping rules for rhDNase (based on an improved lung function response) have been difficult to clinically administer in UK CF centres because of a lack of proven correlation between FEV_1 response and a reduction in exacerbations. Whilst a stopping rule for rhDNase is not supported by the clinical data the converse is true for inhaled mannitol. Data from the inhaled mannitol trials clearly shows that a FEV_1 response at 6 weeks is a very sensitive and specific predictor of the response at 26 weeks. In addition, patients demonstrating any improvement in FEV_1 over the 26 weeks of the study had 59% fewer exacerbations than those that experienced a decline in lung function. A stopping rule based on FEV_1 improvement at 6 weeks is therefore clinically and scientifically validated, appropriate to improve the cost-effectiveness of a treatment, and relevant for patients encumbered with a heavy treatment burden.

In recognising the Committee's concerns of implementing a stopping rule requiring a patient to achieve a 100mL or 5% improvement in FEV1 (absolute or % predicted), the manufacturer proposes to modify the continuation criteria at 6 weeks to a >0% improvement. In doing so, the sensitivity and specificity in predicting response at 26 week is retained. The cost-effectiveness is decreased slightly, but this trade-off is accepted given feedback from senior CF clinicians that a 0% cut off will improve patient acceptance and clinical implementation of the stopping rule.

Patient treatment pathways: As highlighted by the Committee, the treatment of CF is complex. Treatment is tailored to the patient's needs and clinical guidelines reflect an individualised approach to protocols. Prescribed treatments for CF are not captured or available in the UK public record in sufficient detail to be able to derive insight upon which to evaluate a patient treatment pathway. To be able to evaluate the unmet needs of current treatments for adults with CF an independently commissioned survey examined rhDNase and hypertonic saline usage; treatment satisfaction; and how physicians would use inhaled mannitol. The survey captured data from 29 CF respiratory physicians from at least 10 of the 19 adults centres within the England and Wales. The points most relevant for this evaluation are summarised below and full details are provided in the attached report. Of particular note:

- Only 18% of adult patients (aged 18 and over) have never used rhDNase or hypertonic saline and consequently the opportunity for inhaled mannitol to be used as a first line agent is very small.
- About one third of patients are perceived by clinicians to be uncontrolled irrespective of the treatment they are taking. This underlines the level of unmet need which exists in the adult CF population despite the widespread use of existing treatments
- Clinicians see inhaled mannitol as a potentially useful treatment particularly in patients who are not well controlled despite treatment with hypertonic saline and/or rhDNase (50% of the proposed population), and a beneficial option for patients not currently receiving treatment (19%).
- Inhaled mannitol was not perceived as a treatment that will replace existing treatments on a significant scale when those patients are well controlled.
- The % of patients on hypertonic saline who are well controlled that would be considered for a trial on inhaled mannitol is very low (11%).
- Extrapolating these results to the CF population in the UK the proposed potential Bronchitol-treated population would be 1,000 patients. This compares with the 4,000 patients currently estimated to be on rhDNase and the 3,600 patients estimated to be on hypertonic saline**.**

<table>
<tr><th>Pg No</th><th>Section No.</th><th>Statement from ACD</th><th>Comment, clarification and requested modification to the ACD</th></tr>
<tr><td colspan="4">POINTS OF FACTUAL ACCURACY</td></tr>
<tr><td colspan="4">The following points reflect in points of accuracy for correction</td></tr>
<tr><td></td><td></td><td colspan="2">The following points reflect statements or corrections to the preliminary ACD. Please clarify and ./ or correct accordingly.</td></tr>
<tr><td>4</td><td>2.3.</td><td>£0.84 per 40mg caps / £16.88 per day / £236.25 per 14d pack.</td><td>Please be advised and correct that as confirmed by the DH (26th April, 2012) the price of Bronchitol® in England and Wales is:
• Bronchitol Initiation Dose Assessment (BIDA), single use pack containing 10x40mg capsules and 1 inhaler is <u>£8.27</u>*
• Bronchitol® 14 day pack (14-day treatment pack containing 280 x 40mg capsules and two inhalers) is <u>£231.66</u> per 14d pack (equivalent to an average of £16.55 per day; £0.83 per capsule).
• All prices have been updated in the revised model provided (please see below and attachments).

*Note: The BIDA is designed to assess bronchial hyper-reactivity prior to commencing Bronchitol treatment</td></tr>
<tr><td>4</td><td>2.3.</td><td>£0.84 per 40mg caps / £16.88 per day / £236.25 per 14d pack.</td><td>Please be advised and correct that the price of Bronchitol® is at parity to Pulmozyme.
• The currently listed price of Pulmozyme (rhDNase) in England and Wales is: <u>£16.55 per vial (2500 units) per day</u>*
• All prices have been updated in the revised model provided (please see description in the Executive summary) .

*Source: BNF version 63, March 2012.</td></tr>
<tr><td>4</td><td>2.3.</td><td>"Mannitol available as 5, 10, 20 , 40 mg powder caps"</td><td>Please correct: Bronchitol® is formulated as a 40mg capsule of Mannitol only.</td></tr>
<tr><td>6</td><td>3.4.</td><td>"In both trials, participants were offered the opportunity to continue or start mannitol treatment in an open-label phase for a further 26 weeks in order to gain further information on adverse reactions; <u>in DPM-CF-302, there was an additional open-label extension phase of 26 weeks, giving a total of 78 weeks</u>."</td><td>Please restate: "In both trials, participants were offered the opportunity to continue or start mannitol treatment in an open-label phase for a further 26 weeks in order to gain further information on adverse reactions; <u>in DPM-CF-301</u>, there was an additional open-label extension phase of 26 weeks, giving a total of 78 weeks."</td></tr>
<tr><td>8</td><td>3.10.</td><td>"Time period unspecified"</td><td rowspan="2">Please see Manufacturer response, Table 1 of the Clarification Request to the ERG provided 7th April 2011.
By way of clarification the period was <u>over the 26 week time-horizon of the trial.</u></td></tr>
<tr><td>9</td><td>3.13.</td><td>"Time period unspecified"</td></tr>
<tr><td>8</td><td>3.09</td><td>"Following clarification, the manufacturer provided the change in FEV1 between 6 and 26 weeks for the 43 adults who were ineligible , intolerant or inadequately responsive to rhDNase ; this was 147.0 ml, which was significantly different from control (p = 0.02, <u>no numerical absolute values provided</u>)."</td><td rowspan="2">Please be advised that no request was received for these values after the manufacturer submitted this data to the ERG (Clarification request. 7th April 2011; page 3 and figure 2). Please correct with the absolute values as Mean and [95%CI] accordingly:

DPM-CF- 301 Trial (Adult – rhDNase unsuitable)
<table><tr><td>Mannitol:</td><td>155.82 mL</td><td>[95% CI: 97.45-115.13]</td></tr><tr><td>Control:</td><td>8.84 mL</td><td>[95% CI: 82.79-228.85]</td></tr><tr><td>Difference</td><td>146.98 mL</td><td>[95% CI: 23.23-270.74]</td></tr></table>
DPM-CF- 302 Trial (Adult – rhDNase unsuitable)
<table><tr><td>Mannitol:</td><td>179.28 mL</td><td>[95% CI: 39.79-318.76]</td></tr><tr><td>Control:</td><td>-29.32 mL</td><td>[95% CI: -207.88-149.23]</td></tr><tr><td>Difference</td><td>208.6 mL</td><td>[95% CI: -9.34-426.53]</td></tr></table></td></tr>
<tr><td>9</td><td>3.12.</td><td>"Following clarification, the manufacturer provided the difference in the change in FEV1 between 6 and 26 weeks for mannitol in 22 adults who were ineligible, intolerant or inadequately responsive to rhDNase compared with controls; this was 208.6 ml (p = 0.061, <u>no absolute numerical values provided</u>)."</td></tr>
</table>

<table>
<tr><td>10</td><td>3.15.</td><td>"..For the pooled adult population of rhDNase users, the mean change in FEV1 between 6 and 26 weeks for patients receiving mannitol plus rhDNase was 94.1 ml (no 95% CI given). The change was 166.7 ml (95% CI not given) for adults receiving mannitol who were ineligible, intolerant or inadequately responsive to rhDNase. The change was 166.7 ml (95% CI not given) for adults receiving mannitol who were ineligible, intolerant or adequately responsive to rhDNase."</td><td>Pooled data: DPM-CF- 301 and DPM-CF- 302 Trial (Adult - rhDNase users)
<table>
<tr><td>Mannitol:</td><td>68.7 mL</td><td>[95% CI: 18.18-119.23]</td></tr>
<tr><td>Control:</td><td>-25.36 mL</td><td>[95% CI: --79.47-158.42]</td></tr>
<tr><td>Difference</td><td>94.06 mL</td><td>[95% CI: 29.7-158.42]</td></tr>
</table>
Pooled data: DPM-CF- 301 and DPM-CF- 302 Trial Adult – rhDNase unsuitable)
<table>
<tr><td>Mannitol:</td><td>173.06 mL</td><td>[95% CI: 103.57-242.56]</td></tr>
<tr><td>Control:</td><td>6.34 mL</td><td>[95% CI: -90.22-102.89]</td></tr>
<tr><td>Difference</td><td>166.73 mL</td><td>[95% CI: 52-280.59]</td></tr>
</table></td></tr>
<tr><td>8</td><td>3.11</td><td>“In the DPM-CF-301 trial, the manufacturer did not report the proportion of adults considered to be responders using FEV1 criteria for the two subpopulations according to rhDNase use.”</td><td rowspan="3">Please re-state the proportion of responders and non-responders based on 5% (absolute or % predicted) FEV1 or >100 mL improvement at 6-weeks according to +/- rhDNase use in the DPM-CF-301, DPM-CF-302 and pooled trial analysis, with the provided data in Appendix I:</td></tr>
<tr><td>9</td><td>3.14</td><td>“In the DPM-CF-302 trial, the manufacturer did not report the FEV1 responder status for the two subpopulations according to rhDNase use.”</td></tr>
<tr><td>10</td><td>3.16</td><td>“In the pooled analyses of FEV1 response the manufacturer did not differentiate by rhDNase status, and did not submit a statistical analysis of the difference between the two groups. The proportion of adults in the two studies combined who experienced an FEV1 response was 48.3% in the mannitol group and 34.3% in the control group.”</td></tr>
<tr><td>11</td><td>3.18</td><td>Haemoptysis was the most clinically significant adverse reaction in both studies and was observed in 11.9% of adults on treatment with mannitol and 8.5% in the control group in the DPM-CF-301 trial, and in 7.1% and 2.5% respectively in the DPM-CF-302 trial.</td><td>Please restate total haemoptysis rates. These rates for Haemoptysis are from discrete adverse events and have excluded event occurrences that were integrated within the protocol defined pulmonary exacerbation definition. When the haemoptysis events that were recorded as part of reports on exacerbations are included with adverse events from both studies then the total % of adults with haemoptysis was <u>15.5% on mannitol and 17.9% on control</u>. A further listing by +/- rhDNase usage sub-population is provided below.
Adult patients (+/- rhDNase) with Haemoptysis – pooled analysis of DPM-CF- 301 and - 302 Trials
<table>
<tr><th>subgroup</th><th>TYPE</th><th>MANNITOL</th><th>CONTROL</th></tr>
<tr><td>Adults (all)</td><td>n</td><td>207</td><td>134</td></tr>
<tr><td>Adults (all)</td><td>All Types</td><td>32 (15.5%)</td><td>24 (17.9%)</td></tr>
<tr><td>rhDNase -Users/Adults</td><td>n</td><td>122</td><td>85</td></tr>
<tr><td>rhDNase -Users/Adults</td><td>All Types</td><td>20 (16.4%)</td><td>17 (20.0%)</td></tr>
<tr><td>rhDNase -nonUsers/Adults</td><td>n</td><td>85</td><td>49</td></tr>
<tr><td>rhDNase -nonUsers/Adults</td><td>All Types</td><td>12 (14.1%)</td><td>7 (14.3%)</td></tr>
</table></td></tr>
</table>

TRIAL DESIGN, PRIMARY END POINT & FEV1			
Clarification of the trial design, choice in primary endpoint (FEV1 percent predicted) and its calculation as change over time.			
		Trial design: In the protocol for both the DPM-CF301 and DPM-CF302 trials, all subjects were screened based on inclusion/exclusion eligibility criteria. Screening of patients included an evaluation of (bronchial) reactivity to mannitol using the Mannitol Tolerance Test (MTT). This is commercially provided as the Bronchitol Initiation Dose Assessment (BIDA). Patients were then randomised, but were otherwise not treated differently up to this point in the trial. Between 2 and 5 weeks after this initial screening and randomisation visit, a treatment week-0 visit was scheduled. At this visit, baseline measurements were taken, prior to administration of any study drug. Some subjects dropped out between screening and the first visit. This was completely at random and did not disturb the randomisation scheme. Please see schematic of trial design (Figure 2) and consort diagram (Figure 3 and 4) within the MS. The trials were conducted in accordance with appropriate ICH-GCP requirements including blinding and data collection. **Primary end point (Change in FEV):** The protocols for both trials (CF301 and CF302) defined the primary endpoint as the change in absolute FEV1 over the 26 week treatment period. The predefined statistical plan for both studies defined this as the average change in absolute FEV1 observed at week 6, week 14 and week 26 of treatment relative to the FEV1 measured at week 0 (baseline), versus control. The justification for excluding week 0 from the calculation of a treatment effect is that by definition a baseline is needed to be established at treatment week 0 (prior to treatment starting) as a reference point to establish the 'Change from baseline' over the 26 week period. Since this 'Change from baseline' at week 0 (baseline) is 0, it does not reflect a treatment effect and is therefore not incorporated in the average change over the 26 weeks. This methodology for evaluating a change in FEV1 has been previously established for other treatments for CF, for example in evaluating the treatment effect of rhDNase (dornase alfa) on lung function in its pivotal study (Fuchs et al.,1994). All analyses were specified with extensive sensitivity analyses to confirm the primary analysis findings. In other Bronchitol phase II studies, an observed treatment effect of a similar magnitude to that seen at week 6 is evident by week 2 of treatment. Therefore using an average treatment effect from week 6 onwards under-reports the time to a treatment effect, likely to be evident earlier than a first measure at 6 weeks. Please also note that this approach is consistent with that presented in the cost-utility analysis in the MS, whereby Week-0 to Week-6 are assessed as receiving a treatment response (previously stated as >5% improvement in absolute or % predicted FEV1 and / or 100 ml improvement in FEV1).	
6	3.5.	The primary outcome in both trials was the absolute forced expiratory volume at 1 second (FEV1) as measured in millilitres. Both trials reported changes in FEV1 from baseline in the mannitol group compared with the control. <u>The manufacturer's submission noted that the primary outcome was the change in absolute FEV1 over 26 weeks, but at the Committee meeting the manufacturer stated that the a priori protocol-defined primary outcome was a change in absolute FEV1 from week 6 to 26.</u>	**Please clarify in the ACD that:** • **The change in FEV1 is over the 26 week duration <u>of treatment</u>, with measurement of change at 6, 14, 26 weeks relative to baseline (week 0)**.
7	3.9.	"This difference was evident at 6 weeks (<u>although this was defined by the manufacturer at the Committee meeting as baseline</u>) and was maintained over the 26-week double-blind phase."	• The change in FEV1 is over the 26 week duration of treatment, with measurement of change at 6, 14, 26 weeks relative to baseline (week 0). • **"The difference was evident after 6 weeks <u>of treatment</u> and maintained over the 26 week double-blind phase..."**

31	4.10.	"The Committee considered the analysis of the trials. In particular, the Committee was concerned that the manufacturer used the FEV1 value established at the screening stage prior to baseline as a covariate when analysing the randomised control trials. When questioned, the manufacturer did not explain why it had done this. The Committee further noted that the manufacturer had not provided the unadjusted figures for the absolute FEV1 at week 0. The Committee considered that there may have been differences in patients entering the trial, but concluded that any differences would have been compensated by randomisation rather than being adjusted for as a covariate. The Committee was concerned that the manufacturer chose to omit data from weeks 0 to 6 and use data from weeks 6 to 26 only. The manufacturer and clinical specialist explained that this was a common way of designing trials for drugs for cystic fibrosis, that there is often an 'overemphasised' lead-in period, and that using data from week 6 rather than week 0 was a way to mitigate this effect. However, the Committee was not persuaded that the analyses of the trials represented the data accurately and completely."	Spirometry to establish an unadjusted baseline FEV1 was conducted at Visit 1 / treatment Week-0 and not the screening visit. The change in FEV1 is over the 26 week duration of treatment, with measurement of change at 6, 14, 26 weeks relative to baseline (week 0). • **Please remove underlined text due to a misunderstanding : "FEV1 value established at the screening stage prior to baseline as a covariate when analysing the randomised control trials ...than being adjusted for as a covariate "** • **Please consider removing or modifying the underlined text, based on the methodology description above and accepted use in CF trials.**

18	3.35.	Pooled results showed statistically significant results in FEV1 but not exacerbations (only trend difference in non-rhDNase users)	**Please state the non-statistical significance of these results in the context of the available data and clinical significance to patients with CF:** As highlighted in the Executive Summary above, CF is an orphan condition with a low life expectancy characterised by a progressive decline in lung function (FEV1) and frequent respiratory infections (exacerbations) that often lead to hospitalisation. The clinical goal for patients with CF is to prevent further loss in lung function (European Medicines Agency, 2009), which has been shown to correlate with a risk of exacerbation (Liou et al; 2001) and mortality (Stern et al; 2008, Hayllar et al; 1997, Courtney et al; 2007). Although exacerbations still represent a frequent and disabling event for patients with CF, in recent years, incremental improvements in treatment (including the introduction of prophylactic antibiotics) has had some impact to reduce the background rate of exacerbations. Consequently, statistically powering trials in CF patients to show a significant reduction in exacerbations is challenged by their relatively low event rate (at least as needed to show a treatment difference); and the availability of patients from a small orphan disease pool. Therefore, consistent with Regulatory advice at the time, the two Bronchitol® (inhaled Mannitol) registration trials (DPM-CF-301 [n=295] and DPM-CF- 302 [n=305]) were individually powered to show statistically significant improvements in lung function for all patients (children and adults), but the individual studies were not required to be powered to show a reduction in exacerbations. In October, 2011, the EMA provided an initial indication for inhaled mannitol as a treatment in adult-only patients [n=341] and as such the overall statistical power of the trial(s) data to show a difference in primary endpoint was further reduced, as was the ability to demonstrate a statistically significant treatment difference in exacerbation rate (a secondary endpoint). Due to the studies being of similar design and study population, the EMA accepted pooled analysis of patients in their evaluations (EPAR: www.ema.europa.eu). It is therefore of clinical significance that in the pooled registration trials, adult patients treated with Inhaled mannitol, when compared to best supportive of care (BSC +/- rhDNase) demonstrated: • A substantial improvement in lung function (99.5mL, p<0.001) at over 26 weeks that represents a step improvement advancement in the treatment of CF. It is of note that control patients receiving BSC experienced an average ~8mL decline in lung period over the same time period. • This significant improvement in lung function was observed in all patients when added to BSC, regardless of patients comparatively receiving BSC, with (94.1 mL, p<0.008) or without (110.3 mL p<0.005) rhDNase. • The improvement in lung function was sustained to at least 78 weeks in open-labelled extension studies. • In Patients switched from control to inhaled mannitol at 26 weeks, also experienced a substantial return improvement in lung function. After 52 weeks of treatment, these patients had regained similar levels of lung function to those that had received inhaled mannitol throughout the trial. • A lower exacerbation rate, with reductions in protocol defined pulmonary exacerbations (PDPE) in the adult population of 24% (95% CI: 0.51; 1.13), when compared to BSC. • A significant difference in PDPE rates was also observed when compared to patients receiving BSC without rhDNase. Despite insufficiencies in sample sizes and event rate frequencies to satisfy statistical rigour, this consistency in trend was observed in all sub-group.(Rate Reduction: mannitol: 0.38 vs. control: 0.97) • The treatment response with inhaled mannitol showed early. at 6 weeks, for patients experiencing greater than 0% improvement in FEV1, or 5% (absolute or % predicted) and/or 100mL improvement in FEV1 were highly predictive (sensitivity 86.8% and 88.1%) and specific (specificity of 78.2% and 81.1%) of an improved response at 26 weeks, respectively (All patient, ITT analysis).

		(continued from above)	• The overall safety profile of inhaled mannitol was favourable, with the most common side effects being manageable • A significant improvement in lung function and reduction in exacerbations in patients receiving BSC (+/- rhDNase) but experience the most rapid deterioration in lung function (> 2% annual decline in FEV1% predicted per year). Based on pooled data used in the CUA, change from baseline in FEV1% predicted at 26 weeks was -1.10 (95%CI: -3.72-1.52) in patients treated with BSC (+/-rhDNase) and in patients treated with inhaled mannitol: 2.71 (95% CI: 0.54-4.87), with relative exacerbation rates of 1.37 and 1.14 per year, respectively. These perspectives are also shared by 62 European CF specialist clinicians in a consensus statement provided to the EMA supporting a clinical need for inhaled mannitol (Bronchitol). It is of note that the consensus statement included 12 practicing specialist physicians from different centres in the UK (Appendix: Consensus statement supporting a need for Bronchitol® and provided to the EMA)
28	4.6.	"The Committee was concerned about the absence of the trial protocols from the manufacturer's submission, and therefore could not fully understand the design of the trials and their analyses."....."Committee concluded there were significant concerns about the design of the trials and the resulting analyses, and that these factors increased the uncertainty in the results."	**Please restate or remove this statement as contradicts other sections of the ACD and represents an unreasonable 'concern' given the available information provided to the ERG:** Please note that all trials relevant to this submission were (and as acknowledged by the ERG) identified in the systematic literature review. Within these publications, all details of the trial design are presented. Although not previously requested, but by way for completeness and transparency, the final protocols for trial DPM-CF-301 and DPM-CF-302 are provided. It is of contradictory note, that the ERG have stated elsewhere that the DPM-CF-301 and DPM-CF-302 trials were well designed, of high-quality, and provided a large combined study population (Section 3.3, page 18 of the ACD). As previously described in the MS and above, the trial design was robust and the analyses likewise. It is not clear how the studies could be considered inadequate in design or analysis.
29	4.8.	"The Committee questioned the selection of FEV1 measurements in the trial and in the economic model. It noted that the primary outcome in the two trials was absolute FEV1, but that the measurement of lung function used in the model was FEV1% predicted."	**Please consider adding that the model data used FEV1% predicted as this metric is preferred by experts within the CF community.** Whilst it is recognised that FEV1 criteria was mentioned in the original Scoping document prepared by NICE, expert opinion at from the CHMP's Scientific Advisory Group (SAG) meeting in September 2011of the EMA recommended and endorsed the use of % predicted FEV1 over absolute FEV1: "***Q4.*** *The change in FEV1 can be measured as the absolute change from baseline (in litres), the relative change (as percent change from baseline), or the absolute change in percent predicted FEV1. While the predefined primary endpoint in the two phase 3 pivotal studies is the change from baseline in FEV1 (mL) in the response to the CHMP grounds for refusal the results are discussed as the relative change in FEV1 predicted of normal. While using FEV1 (% predicted) is endorsed if children and adolescents are considered it is believed that the results to be taken into consideration are those corresponding to the absolute change in percent predicted FEV1. Could the experts provide their opinion on the above issue?* **Experts' response:** The assessment based on relative % predicted change is better than the use of absolute change in mL, the latter being not considered appropriate for the study. However, the experts also noted that the absolute % predicted change would have been even better." It is also recognised that FEV1 % predicted has been the chosen as the preferred method of reporting lung function in adults by the UK CF Trust in their Annual Registry Report, and is recommended by the EMA in designing clinical trials for patients with CF (European Medicines Agency, 2009). A copy of the minutes from the SAG meeting at the EMA and hyperlinks to recent UK CF Trust reports are provided in the Appendices.

29	4.8.	".....The Committee heard from clinical specialists that both absolute FEV1 and FEV1% predicted measurements are used in clinical practice, that between 75 and 100 ml absolute FEV1 change is clinically meaningful, and that FEV1% predicted is used for children and to compare adult patients with their peers. The Committee noted that in the trials patients who did not meet the definition of response stopped treatment at 6 weeks.."	**Please remove underlined text as incorrect:** Patients that that did not respond at week 6 of treatment were examined as part of specified statistical analysis, but were not stopped from continuing in the trial. The trial did not have a stopping rule.
30	4.9.	"The Committee discussed the use of imputed height calculations for the FEV1% predicted data, but the manufacturer was unable to provide information on how many individual measurements were adjusted in this way, thereby increasing uncertainty about the robustness of the manufacturer's clinical outcomes."	**Please remove underlined text as non-relevant to the adult population as incorrect:** The eligibility criteria for FEV1 % predicted were calculated with actual heights for all patients at screening. It is only when the efficacy endpoint of FEV1 % predicted was calculated that data for heights were imputed (from measurement taken at screening). As this submission is for adults only, the imputation method used (from growth charts) would be considered irrelevant to adults as they do not have growth charts, and growth would be considered negligible over the study duration.

POINTS OF IMPORTANT CLINICAL NOTE			
Points of clinical importance, that highlight the medical advancement and value that inhaled mannitol brings to patients with CF.			
7	3.6.	"Protocol-defined pulmonary exacerbations (PDPE) were defined as pulmonary events with four or more pre-defined symptoms or signs needing intravenous antibiotics. Reductions in the frequency of both PDPE and hospital care were measured in both trials."	**Please consider in the context of CF:** This (Fuch's) criteria reflects a stringent criteria for objectively classifying an exacerbation event relative to many other criteria used to measure exacerbations in trials of patients with CF (Dentice et al., ECFS, 2012). In clinical practice, patients that have less than 4 criteria of a defined "exacerbation event" would still require medical intervention and consume healthcare resources. These criteria would also have a significant impact on patients and their carers. Using the Fuch's criteria therefore reflects an underestimation of the clinical, economic and patient (humanistic) impact of exacerbations experienced by CF patients within the NHS. This objective criteria was selected as a conservative approach to evaluating the benefits of Inhaled mannitol to reduce exacerbations, and would likely to thereby under-value the benefits of reducing exacerbations in actual clinical practice.
8	3.09	"Following clarification, the manufacturer provided the change in FEV1 between 6 and 26 weeks for the 43 adults who were ineligible , intolerant or inadequately responsive to rhDNase ; this was 147.0 ml, which was significantly different from control (p = 0.02)"	**Please consider removing these comments in the context of revised label:** The subgroup of patients in the study referenced in these comments were originally targeted in the MS because the label applied for with the CHMP was; " add-on therapy to rhDNase or in patients intolerant to, or inadequately responsive to rhDNase". Following advice from the CHMP's Scientific Advisory Group that this definition was not clinically appropriate the final label approved by the EMA was '…add on therapy to best standard of care'. The subgroup that is intolerant to or inadequately responsive to rhDNase demonstrated improvements in lung function similar to other adult sub groups but the sample size was small and not predefined in study CF301, and was the subject of NICE concerns in the preliminary ACD. It is no longer in line with the Bronchitol approved label and has therefore been removed from the base case proposition. These perspectives are also shared by 62 European CF specialist clinicians in a consensus statement provided to the EMA in support of inhaled mannitol (Bronchitol®). The consensus comprised of 12 physicians from the UK (Appendix: Consensus statement supporting a need for Bronchitol and provided to the EMA)
9	3.12.	"Following clarification, the manufacturer provided the difference in the change in FEV1 between 6 and 26 weeks for mannitol in 22 adults who were ineligible, intolerant or inadequately responsive to rhDNase compared with controls; this was 208.6 ml (p = 0.061)."	
10	3.15.	"..For the pooled adult population of rhDNase users, the mean change in FEV1 between 6 and 26 weeks for patients receiving mannitol plus rhDNase was 94.1 ml (no 95% CI given). The change was 166.7 ml (95% CI not given) for adults receiving mannitol who were ineligible, intolerant or inadequately responsive to rhDNase.	

19	3.36.	The ERG indicated that "hypertonic saline seemed superior to mannitol in reducing pulmonary exacerbations, but the ERG did not attempt a comparison because the specific outcome measures for pulmonary exacerbations in the studies were different" (NICE acknowledge statistically significance for mannitol in the subgroup ineligible for rhDNase...).	**Please consider in the context of CF: Comparing the improvement in exacerbations seen in the one long term hypertonic saline study versus those seen in the Inhaled mannitol trials should be set in the context of the patient demographics.** Of the patients in the hypertonic saline study, 79% tested positive for pseudomonas whilst only 12% were taking regular inhaled tobramycin and only 6% received inhaled colistin. In comparison to the Inhaled mannitol trials, 45% of adult patients were positive for pseudomonas and 56% of all patients were on either inhaled tobramycin or colistin. The Inhaled mannitol trials represent contemporary practice, and a population typically found in UK clinics where 38% have chronic peudomonas infections and 79% of these infected patients receive inhaled antibiotics [UK CF Trust Registry Report, 2010]. The population studied in the hypertonic saline study does not exist in today's UK clinics. In the hypertonic saline study, there was almost double the rate of pseudomonas positive patients and yet only a very small proportion of them treated with inhaled antibiotics. It should not be assumed that the results of this study could be repeated in a UK CF patient population and the results should not be compared to those achieved in the Inhaled mannitol trials. It is also important to note that by the age of adulthood the majority of patients have trialled hypertonic saline in the UK (See patient treatment pathway section below). Of those patients still receiving treatment, many are receiving limited benefit from it (uncontrolled), with the majority of CF patients having stopped receiving it (due to medication burden) or requiring to add –on rhDNase due to a lack of treatment effect . These perspectives are also shared by 62 European CF specialist clinicians in a consensus statement provided to the EMA supporting a clinical need for inhaled mannitol (Bronchitol®). The consensus comprised of 12 physicians from the UK (Appendix: Consensus statement supporting a need for Bronchitol and provided to the EMA)

31	4.11	The Committee noted the Cochrane review of hypertonic saline for cystic fibrosis, and the apparent improvement in pulmonary exacerbations and quality of life relative to the use of isotonic saline, and heard that the clinical specialists considered the review to be well-performed and valid. The Committee considered the heterogeneity of the studies available for hypertonic saline and the model presented by the manufacturer. It noted that the outcome measures for pulmonary exacerbations used in the review of hypertonic saline treatment were different from those used in the mannitol trials. The Committee acknowledged that there was little evidence to compare hypertonic saline with mannitol, but recognised that, although not within the context of the marketing authorisation, mannitol may replace hypertonic saline in clinical practice in the UK.	**Please revise underlined text to reflect the weaknesses in extrapolating this single trial, representing outmoded practices and a low background treatment with antibiotics, to contemporary UK practice:** Whilst the manufacturer agrees that the Cochrane review of hypertonic saline was well performed and valid, we disagree that the findings can be applied to the adult population of CF patients in the UK. The review concluded that there was no evidence that hypertonic saline had a long term effect on lung function but it was more positive about the effect on exacerbations. The impact on exacerbations may in part have been due to a higher background exacerbation rate arising from high rates of pseudomonas positive patients and markedly less aggressive antibiotic therapy used in the trial patients compared to demographics of the patients in the mannitol studies. The relevance of the finding on exacerbations to current patients of UK clinics is debatable for the same reasons . The manufacturer considered at some length whether to propose that Bronchitol treatment be limited to patients who have had a recent trial with hypertonic saline in order to address the concern from NICE that inhaled mannitol might replace hypertonic saline in clinical practice. The manufacturer commissioned an independent survey (see patient treatment pathway section below) of adult CF clinicians in England and Wales to seek their views on hypertonic saline usage and whether inhaled mannitol (Bronchitol) would replace hypertonic saline, and also consulted with senior CF clinicians on how such an eligibility criteria might be viewed. Following these investigations we propose that the eligibility criteria for inhaled mannitol should include the words: "*Bronchitol should only be used in those patients who have already been trialled on hypertonic saline and found to be inadequately responsive or those whom are not deemed suitable for treatment with hypertonic saline (4ml 7% twice per day) by the treating clinician*The manufacturer notes the concerns of NICE that mannitol might replace hypertonic saline and if NICE deems it necessary would accept eligibility criteria that recommended use of Bronchitol in patients who were found to be inadequately responsive to, or unsuitable for treatment with hypertonic saline. This would reinforce that Bronchitol is positioned as a treatment of last resort in CF. The manufacturer suggests that care has been taken to ensure any eligibility criteria do not mandate that all patients receiving inhaled mannitol must use hypertonic saline first for the following reasons: • Any mandate would have to include the appropriate dosing shown to be clinically effective and despite ready availability and low cost this dose (4ml 7% BD) is not widely used. The patient treatment pathway survey found that whilst hypertonic saline usage is fairly common in CF adults, its usage at a dose that has been proven to reduce exacerbations in an RCT, is much lower. No qualitative information was collected in the survey to find out why hypertonic saline is chronically under-dosed but the comments from the clinician and patient during the first NICE appraisal meeting suggest that poor tolerability is a key factor. Patients cannot be forced to take the correct dose so to have this mandated in a recommendation would be unrealistic. • CF clinicians will not switch patients who are well controlled on HS to Bronchitol so the financial risk of not mandating the use of hypertonic saline is low. The treatment survey indicated that of those patients who were considered to be well controlled on hypertonic saline (4ml 7% BD), only 11% of them would be considered for a trial with Bronchitol. This equates to less than 50 patients across all adult centres in England and Wales. • Senior CF clinicians would not support the mandated use of hypertonic saline (4ml 7% BD) as it has not been shown to be effective in a UK patient population on best standard of care, and has not had its safety and efficacy profile reviewed by any regulatory authority worldwide.

POINTS OF MODEL CLARIFICATION			
Clarification and corrections in the accuracy of the data on the Cost-Utility Analysis (CUA) within the preliminary ACD are highlighted. In acknowledging the ERG comments on the model, a revised base case model has been produced to reflect the framework and parameter modification proposed by the ERG, with additional data derived from the actual patient-level data. The model has also been revised to present two patient populations in which inhaled mannitol provides a significant clinical benefit for CF patients that have the most unmet need. • **Patients receiving Best Supportive Care (BSC) without add-on rhDNase.** • **Patients receiving BSC (+/- rhDNase) experiencing a greater than 2% decline in FEV1 percent predicted per year.** In addition, the manufacturer has consulted with CF clinicians about NICE concerns that the stopping rule proposed was unlikely to be adhered to. As a result a 0% improvement in FEV1% predicted at 6 weeks is proposed as a stopping rule in order to assist clinical implementation. A prior trial of hypertonic saline may also be required as local practice dictates.			
11	3.20.	The model assumed lifetime treatment with mannitol. The analysis had a time horizon of 100 years, at which point all patients will have died.	Please see in the analysis report provided of the revised proposition the impact of varying the time-horizon in the model (100 years, 50, 10 and 5 years), and consequence to ICER results to the base case.
12	3.22	"The manufacturer did not use clinical effectiveness data from the DPM-CF-301 and DPM-CF-302 trials other than to obtain baseline values and some transition parameters; instead, the manufacturer derived transition parameters from the literature and from the commissioned BioGrid study, using regression analysis"	**Please revise statement to: "The manufacturer did not use a simple cohort approach to model the clinical effectiveness from the DPM-CF-301 and DPM-CF-302 trials, but rather used relevant clinical effectiveness data derived from the trials to build a patient-level simulation through regression analysis . These data included baseline values etc...." :**As detailed in the MS, the ACD commentary (section 3.22 and 3.29) and further below, the model was based on a Markov health-state transition framework, implemented as a patient-level simulation model. By the nature of this construct, regression analysis was required to build the characteristics of a patient transitioning through the model. Whilst the trial cohort were not exactly modelled, all relevant clinical effectiveness data were employed from the trials to develop the model in a form that lent itself more effectively to the appropriateness of the patient population and decision problem. This approach was deemed appropriate by the ERG (Section 3.39 of the ACD) to model the complexities of treatment; variability of patient phenotype; disease progression; response and evaluable patient population size.
14	3.24	"The manufacturer included costs for concomitant medications (mostly antibiotics) for both groups, and used a mean cost of £3253 in the mannitol group and £2972 in the control group. Nearly all patients were admitted to hospital at least once, and approximately 40% had a community visit during the 26- week randomised phase of the trial. Costs of pulmonary exacerbation were taken from the trial data. For patients receiving mannitol, the mean total cost of medications, community visits and hospitalisations without a PDPE in the 26-week trial period was £4391, and with a PDPE the cost was £12,852. For patients in the control group, the mean total costs without and with a PDPE were £4664 and £10,354 respectively."	**Please note that in acknowledging the modifications suggested by the ERG, a revised model was produced.** In this updated model, the total 6 monthly CF costs (including concomitant medications, visits and hospitalisations) were derived by health state (i.e. being improved in respiratory symptoms or not) but not by treatment arm. These costs have now been derived for the base propositions of a non-user sub-population and 2% decline in FEV1% predicted sub-population. For exacerbation costs, the model framework is slightly different. We calculated this cost as the difference in 6-months costs between patients who had 1 PDPE during the 26 weeks versus all patients who had 0 PDPE during this period. As we believe the cost of the PDPE itself would not differ if a patient was on rhDNase or not. We have used the all adult data to calculate this cost (i.e. this remained unchanged from our original submission).

<table>
<tr>
<td>16</td>
<td>3.28</td>
<td>"Following a request from the ERG the manufacturer provided scenario analyses taking into account reduced adherence to treatments, which reduced the costs in the mannitol group."</td>
<td>Please add results based on testing a range of 30-70% compliance rates for CF treatment observed in clinical practice: A sensitivity analysis was performed and provided within a clarification request to the ERG, examining reduced adherence to treatment based on returned medication at visits within the trial (>85%). However, data was not available to effectively model outcomes relative to adherence rates beyond that provided as an estimate in returned medication within a trial setting. As highlighted in the MS, published compliance rates for treatment ranges from 30-70% in patients with CF which is associated with a deterioration of lung function (Havermans et al., 2008; Sawicki et al., 2008; Harrop et al., 2007; Wilcken et al., 2007; Schreyögg J, et al., 2006). Adherence worsens with age and disease severity (Horvais et al., 2006). To provide the ERG with a sense of the impact this would have on the model, a scenario whereby the costs of treatment are reduced 30-70% (based on poor compliance), with outcomes unchanged.
<table>
<tr><th>Variable</th><th>Bronchitol cost (£)</th><th>Bronchitol QALYs</th><th>Control cost (£)</th><th>Control QALYs</th><th>Incremental Cost (£)</th><th>Incremental QALY</th><th>ICER (£)</th></tr>
<tr><td>Compliance 30%</td><td>175,067</td><td>11.84</td><td>171,619.4</td><td>11.27</td><td>3,447.2</td><td>0.57</td><td>6,326.8</td></tr>
<tr><td>Compliance 70%</td><td>179,322</td><td>11.84</td><td>171,619.4</td><td>11.27</td><td>7,702.4</td><td>0.57</td><td>14,136.7</td></tr>
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<tr>
<td>35</td>
<td>4.17.</td>
<td>"It noted that the modelling of treatment effect used FEV1% predicted, despite the trials' primary outcomes being absolute FEV1, and that the FEV1 measure had not been incorporated within the structure of the model. The manufacturer stated that the FEV1% predicted was used because it was considered the most appropriate outcome for the children in the trials, and the Committee understood that the manufacturer did not change the model when the population changed to adults only."</td>
<td>Please modify the underlined statement accordingly or remove: In addition to comments made in Section 4.8 above, regarding the appropriateness of choosing FEV1 % predicted, a decision to incorporate FEV1 % predicted within the model was informed by the advice of an independent clinical and health economic advisory board. This advisory board informed the model development prior to MS being submitted to NICE and was not a post-submission correction. In preliminary analysis using absolute FEV1 this would not have significantly influenced the results, and FEV1 % predicted was considered the most appropriate metric to represent clinical practice.</td>
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35	4.18.	"The manufacturer had assumed that mortality was a function only of FEV1% predicted and the presence or absence of Burkholderia cepacia infection, as well as age and sex. The Committee was aware that other studies, including one using UK data, demonstrated a wider range of variables associated with mortality in cystic fibrosis, and particularly noted that body mass index was not included in the manufacturer's mortality calculations, whereas it was a parameter for other variables within the model. In addition, the Committee noted that the hazard ratio associated with Burkholderia cepacia infection was significantly greater in the manufacturer's analysis than in multivariate survival analyses of UK and US registry data."...."The Committee acknowledged that there was little evidence that mannitol would alter other factors associated with mortality, but concluded that the mortality rate within the manufacturer's model may not accurately reflect mortality in cystic fibrosis."	**Please add that as described in the MS and BioGrid report, the survival model used by the manufacturer examined these listed covariates and found only FEV1% predicted to be significantly influential. However, relative risks associated with Bcc infection were varied in the deterministic Cost Utility Analysis (CUA) sensitivity analysis (page 184 of the MS) and were confirmed to have minimal impact on ICER results.** . It is true that many factors have been associated with increased mortality, however as described in the MS and provided in the BioGrid report, the survival models produced by BioGrid included covariates of FEV1% predicted, BMI, gender and exacerbations. Only FEV1 % predicted was shown to be a significant factor and therefore considered as a covariant for the regression model. The updated version of the model includes this regression model. Specifically regarding the relative risk of Bcc infection used in the model, a sensitivity analysis was conducted (and as shown in Table 95, pg 184 of the MS) demonstrating that testing the relative risk to the stated upper (10.75) and lower (1.00) boundaries did not have a significantly influential impact on the ICER result.
38	4.23.	"The Committee concluded that the economic model had not incorporated the specific impact of adverse reactions on the health-related quality of life of people with cystic fibrosis and that their inclusion could increase the ICER."	**Please remove this text as factually incorrect:** Adverse events between the Inhaled mannitol and control groups in the adult population showed no significant differences that would impact on quality of life. The rates stated earlier in this ACD for haemoptysis indicating an apparent difference favouring control were from discrete adverse events and excluded event occurrences that were integrated within the protocol defined pulmonary exacerbation definition. As described in detail in response to Section 3.18, when the haemoptysis events that were recorded as part of reports on exacerbations are included with adverse events from both studies then the total % of adults with haemoptysis was 15.5% on Inhaled mannitol and 17.9% on control. Neither a clinical nor economic advantage has not been suggested in the model for patients that experienced lower haemoptysis rates associated with Inhaled mannitol treatment. No other safety events were noted of significant differential clinical or economic impact between strategies.

38	4.24.	"The Committee considered the relationship between FEV1% predicted and lung transplantation in the model, however, the relationship could not be fully explained by the manufacturer or the ERG. The Committee heard from the ERG that the proportion of patients alive at age 55 predicted by the model (15%) was greater than that found in the UK cystic fibrosis population. The Committee heard from the ERG that approximately 2% of patients with cystic fibrosis are still alive at age 50, but the clinical specialist questioned the validity of this number from Cystic Fibrosis registry data. The Committee questioned the assumption that the total QALYs gained were higher for those taking mannitol alone than for those taking mannitol as an add-on treatment. The Committee was concerned that when the relative risk for the individual subgroups was used in the model, more QALYs were gained with mannitol in the rhDNase non-user group than in the rhDNase user group.....The Committee concluded that there were significant issues with the internal validity of the model, and that this would increase the uncertainty around the ICERs."	**Please note base case revisions of the model have acknowledged the ERGs commentary on the model and are provided in detail in the analysis report in the Appendices:** In the revised model, a relatively high proportion of patients are still alive at the age of 55 (approx. 25%). However, this is an adult population, i.e. the relatively healthy population compared to the ALL population that includes children. The average age patients enter the model is 30.5 years. In looking at Table 1.2 in the 2010 CF Trust Registry Report (attached) about 60% of patients have already died at this age. Approximately, 10% of these patients dies above the aged of 55 years. Taking this 10% as the proportion of the 40% still alive at aged 30 years, one would expect that roughly 25% (10%/40%) of patients reach the age of 55 or above in UK practice.
41	4.29.	"The Committee considered that the factors likely to have the most effect in the model were the duration of the effect of mannitol, the relationship between measured outcomes, health-related quality of life and mortality, and the baseline FEV1, but it concluded that only more extensive sensitivity analyses would allow a better understanding of the uncertainty around the ICERs."	**Please remove underlined text or clarify specific sensitivity analysis omitted:** As detailed in the MS, an extensive sensitivity analysis was undertaken by the manufacturer and a tornado diagram (pg 186), with full disclosure of the parameters that were considered to significantly influence the model were provided. A similarly extensive sensitivity and scenario analysis has been conducted as part of the revised base case proposition and is attached to this response. This includes duration of treatment effect, the relationship between FEV1 and exacerbations, QOL and mortality. It is not clear what additional sensitivity was requested.

39	4.25.	"The Committee was also aware that the model was sensitive to the baseline utility with the ICER increasing as the baseline utility decreased. The Committee was concerned about the use of HUI2 data rather than the EQ-5D preferred by NICE, noting that there are 8000 health states defined by the HUI2 questionnaire, as opposed to 243 defined by the EQ- 5D. The Committee noted that this may account for small changes in quality of life observed in the trial and result in increased uncertainty about valuing quality of life with cystic fibrosis in the long term. The Committee concluded that it was not convinced that the health-related quality of life of the health states had been appropriately valued and incorporated into the model, and that this led to increased uncertainty around the calculated ICERs for mannitol compared with best standard of care."	**Please add that sensitivity analysis conducted on utilities in the MS model were not significantly influential to the ICER outcome. Where influential, the selected utilities in the base case were considered conservative as shown in the tornado diagram (pg 186) with ICER results being reduced rather than increased. In acknowledging the ERGs comments, in the revised base case model some of this uncertainty has been removed by adopting a framework of using common utilities for health states.** As highlighted in the Manufacturer's comments on the Scoping document, the manufacturer recognised the challenges with incorporating utilities in the CUA, but these were not taken into account: Scoping document comments from the Manufacturer: "we believe that generic indicators of quality of life such as the SF-36 and instruments measuring utility scores are inappropriate for a cost-effectiveness assessment in CF. Presumably because patients with CF have grown accustomed to their condition (i.e. "condition coping"), they do not report a lower quality of life score compared to a general population control group [Wahl et al; 2005]. With the high starting scores reported in CF, ceiling effects give an underestimation of the true impact on patient perceived quality of life. Furthermore it is unlikely that using the EQ-5D instrument would be any more sensitive in picking up changes in Quality of Life than the HUI2 used in the studies. *[This was also agreed by the committee in Section 4.25 of ACD].* Conversely The CFQ-R outcomes inform clinical practice about the effect of disease progression and is a widely accepted and validated tool for use in patients with CF [Quittner et al; 2005], but with a cautionary note that the CFQ-R was not designed to have optimal sensitivity to report patient perceived quality of life. Patients with CF grow up with the disease. They will not readily express needs they are not (yet) aware of (latent needs) because they have adapted to their condition. The development of the CFQ-R did not include the techniques used to elicit latent needs, so it is unlikely that all items reflecting the highest needs of patients were incorporated in the CFQ-R. In addition, questions such as "Have you had to cough up mucus" and "Have you been coughing during the day" are likely to be inappropriate to reflect improvements associated with mucoactive therapies such as Inhaled mannitol. In the absence of an accurate HRQoL measure, we proposed the use of life-years gained instead. This measure reflects a need accepted by society: to prolong the lives of CF patients. Importantly, the sensitivity analysis provided in the MS (p186) shows conservative estimates around utilities were selected in the base case, with greater reductions in ICER likely if other published utilities were selected. In the revised base case models provided to NICE (attached), the framework has been altered to reflect common utilities (and costs) for healthcare states to remove some of the uncertainty around a treatment effect on utilities. In addition, Life Years Gained (LYG) have again been provided as suggested by the manufacturer within the original scoping document.

METHOD AND CHOICE IN EXTRAPOLATING LONG-TERM OUTCOMES

As detailed in the MS, the ACD commentary (section 3.22 and 3.29) as well as within this response (sections relating to **POINTS OF MODEL CLARIFICATION** and **REVISED COST-UTILITY ANLYSIS & PROPOSITION**), the CUA was based on a Markov health-state transition framework, implemented as a patient-level simulation model. For the purposes of extrapolating a life-time experience for CF patients, beyond that captured over the trial period, a suitable source of longitude, patient level data was required. Whilst the UK CF Trust registry collects some of the data required, the data reflects a cross-section of a dynamic cohort, at a single period of time. It therefore prevents an ability to query the data at a patient-level, over the life-time of a patient. Whilst the manufacturer examined many sources of data, a limited number could provide this level of insight to generate sufficient granularity to construct regression analyses to populate the CUA. In selecting the BioGrid data, a trade-off in using a non-UK source of data was made with a view to producing a more robust model with a greater level of data integrity. The manufacturer is concerned that tThis desire to provide NICE with the best available data at the time and its investment in commissioning a de novo analysis of the only available data set with longitudinal patient level data has failed not been recognised by the Committee.

Comparability of the BioGrid data to UK clinical practice: The BioGrid data represents information on over 2300 CF patients, with 39119 records of lung function, patient characteristics and admission records collected since 1974. The BioGrid dataset comprises of 3 hospital databases and four registry databases related to CF treatment in Australia (see MS for full details of the data dictionary). The patient population in the dataset would be considered comparable to that typically seen in the UK.

		BioGrid: (N=389)	*UK CF Trust (2010) (N=7937)*	*BioGrid: (N=224)*	*UK CF Trust (2010) (N=4406)*
Male	**Mean**	50%	53%	50%	55%*
Age (Yrs)	**Median**	12.5	17	23.6	
	25th Perccentile	17.5	-	18.7	-
	75th Percentile	26	-	31.7	-
	Mean				28.5*
	Lower Range		0		16
	Upper Range		79		79
FEV1% predicted	**Mean**	67.5	72.34	60.2	66.34*
	SD	22.6		22.7	
	Median	68.6	74.2	59.4	
	25th Perccentile	50.8	53.5	41.5	
	75th Percentile	86	90.2	79.2	
BMI	**Mean**	19.6	34.5*	21.2	-
	SD	3.3	-	2.9	-
	Median	19.4	-	20.8	21.8*
	25th Perccentile	17.3	-	19.3	19.8
	75th Percentile	21.8	-	22.7	24.1

- Median age of death in Australia (cited within the CF Trust Registry Report, 2009) was 26.7 years in 2009 and 30.3 years in 2008.
- Median age of death in the UK (cited within the CF Trust Registry Report, 2010) was 29 years in 2010 and 27 years in 2009.
- Australian CF trust data indicates that in adult patients, current usage* of rhDNase would be 50.8%. This would be expected to be similar for patients within the BioGrid dataset.
- UK CF trust data indicates that in adult patients, current usage* of rhDNase would be 48.2%.
- *There is reasonable consistency in the general patient characteristics between the two datasets.*
- Based on clinical society guidelines, Australian practice would also be seen to be similar to that practiced in the UK (as opposed to that conducted in US for example).
- It is therefore considered that since the BioGrid patient population may be considered similar to the UK patient population, and as is clinical practice, the data reflecting life-time experience of living with CF would also be generalisable to the UK setting also.

*Adjusted mean, using mid-point estimates reported by the CF trust. In using this method, the data may reflect slight differences to that within the registry. Due to the time restraints the data from the BioGrid dataset was not able to be analysed as matched means / medians to fit with the Trust data,

Evaluating characteristics of patients that experience a >2% annual decline in FEV1% predicted: In additional analysis of adult patients in the BioGrid data, the annual rate of decline in FEV1% predicted was evaluated by number hospital admissions (exacerbations) per year and annual days spent in hospital (as a consequence of exacerbation). A trend is observed, consistent with that observed by others (Liou *et al.,* 2010; Schluchter *et al.,* 2006; and Taylor-Robinson *et al.,* 2012), of an increasing rate in annual decline in lung function being associated with increased numbers of exacerbations and hospital days per year

- In analysing hospital days in the BioGrid dataset, the average change in FEV1% predicted was calculated as the difference between the last and first available FEV1% predicted measurements divided by the difference in ages between these measurements.

Actual Decline in FEV1% predicted

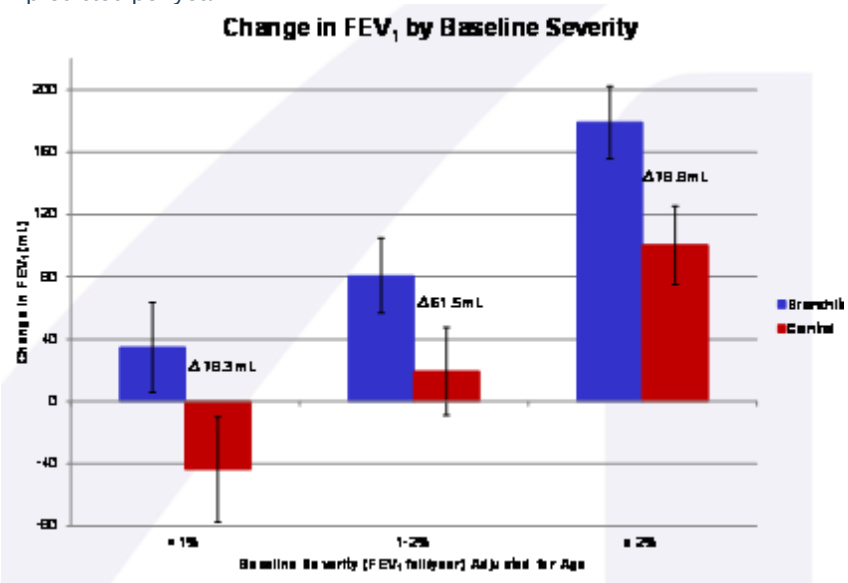
% decline in FEV1% predicted per year	All	
	N	HospDay Mean
< 2%	194	9.3
1% to 2%	57	9.1
< 1%	208	4.8
All	459	7.2

Decline in FEV1% predicted based on a modified rule (100%-[baseline % predicted FEV1]/age)

% decline in FEV1% predicted per year	All		All		
	N	HospDay Mean	N	#Admiss/yr Mean	#Admiss/yr Median
< 2%	224	8.6	174	1.7	0.6
1% to 2%	79	6.5	194	1.2	0.5
< 1%	220	4.5	155	0.8	0.2
All	523	6.6	523	1.3	0.4

- To enable this data to be applied to the trial pooled data (with a limited patient medical history to be able to evaluate a historical rate of lung function decline), patients were assumed to have a FEV1% predicted of 100% at birth, and based on the age of the patient, were categorised as having a decline in lung function as <1%; 1-2% or >2% annual decline in FEV1% predicted. As shown by comparison of hospitalisation day per year, in using this modified rule, the distribution only slightly shifts between decliner categories, however the trend of increased decline in lung function being associated with increased exacerbations is preserved.
- Since hospital days are poorly transferable to other healthcare systems, admissions were examined as proxy for exacerbations (see comments relating to point 3.40 below). Similar to hospital days, an increased decline in lung function is associated with an increased annual rate of hospitalisation (exacerbations).

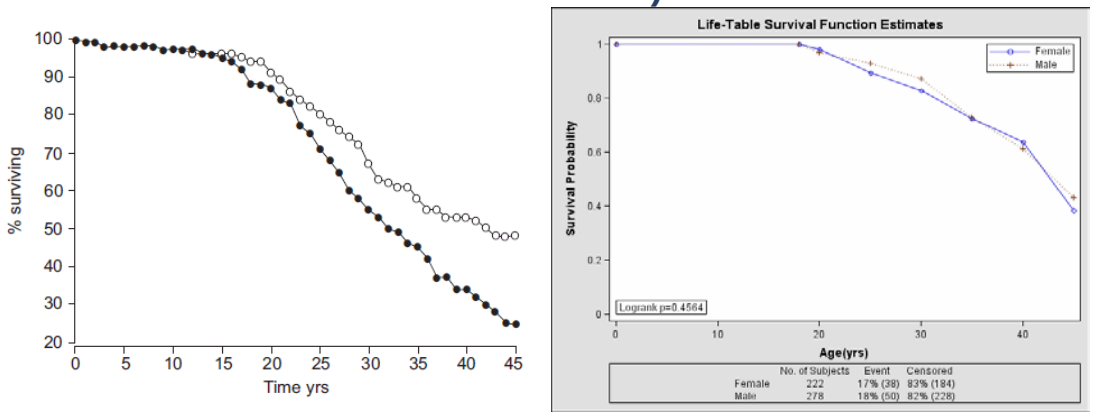
- It is clear from this data and others, that patients with a greater than 2% annual decline in FEV1% predicted represent a significant unmet need. In evaluating the pooled adult trial data it can be seen that patients with the greatest unmet need also show the greatest treatment benefit when receiving inhaled mannitol. Therefore a revised proposition has been formed for the treatment of patients with greater than 2% decline FEV1% predicted per year



- In forming eligibility criteria in this way, also presents consistency with UK clinical practice, as we understand from discussions with the CF community that similar criteria are being formed to evaluate the rationalisation of new treatments in CF, on the basis of an annual decline in lung function.
- Further details of the sub-population clinical and economic outcomes are presented within the CUA report provided with this submission.

21	3.40.	"The ERG questioned the manufacturer's use of Australian BioGrid data for transition parameters and hospitalisation costs, which may not be generalisable to the UK."	**Please clarify that all costs in the CUA are derived from UK sources and only the exacerbation event rate was considered transferable from the BioGrid dataset to the UK practice :** The BioGrid data has used hospital admission as an indication of a significant exacerbation requiring medical intervention. As stated in the BioGrid report provided with the MS, 95% of admission to hospital are due to exacerbations and the remaining 5% of admissions of patients are received with severe disease which a minor exacerbation would trigger. In practice these admission rates reflect a need for medical intervention and medical resource utilisation that would if anything disfavour mannitol treatment in the CUA given the demonstrated treatment effect to reduce exacerbations and thereby undervalue the benefits of inhaled mannitol. Please note that all costs in the CUA are derived from UK sources and only the exacerbation event rate was considered transferable from the BioGrid dataset to the UK practice given that practice and patient population were shown to be comparable to that of the UK (see above).
21	3.41.	"The ERG was concerned about the several assumptions made by the manufacturer about pulmonary exacerbations, namely the narrow confidence intervals around the baseline rate based on the BioGrid data used in the deterministic sensitivity analysis, and questioned whether it applied to a UK population."	As may be expected, the CUA demonstrated a reasonable degree of sensitivity to parameters relating to exacerbations. Sensitivity was tested on the baseline exacerbation rate, the relative risk (RR) of experiencing an exacerbation over 30 years old; the RR of exacerbation if the patient had experienced an exacerbation in the prior year; and the RR of exacerbation with inhaled mannitol - treatment responder effect. As described in the MS, the latter was recognised as having the most influential effect on the model. The addition of a stopping rule at 6 weeks was also shown to reduce this variability. An additional scenario analysis was conducted based on a recent publication (Bradley *et al.,*2010), indicating that the UK exacerbation rate was higher (1.5 exacerbations per year) than that observed in the BioGrid data. In the BioGrid population using proposed methodology proposed by the ERG, the exacerbation rate was 1.01 per year. The model was tested with both including- and excluding an increased risk of pulmonary exacerbation in the previous year. When this increased exacerbation rate and RR for a previous exacerbation were combined, the CUA produced a significant reduction in the ICER to close to £30,000 per year. In additional analysis conducted by BioGrid, the occurrence of a hospital admission (used as indicator for exacerbation, see BioGrid description in comments relating to section 3.40) in a prior quarter was significantly correlated with having an event in the following quarter. Consequently, in combining an increased exacerbation rate seen in UK practice with the RR for a previous exacerbation, would appear consistent with that seen in clinical practice and in not including it in the base case represents a conservative option. This has consequently been incorporated within the revised base case based on the DPM-CF-302 trial data (RR= 1.59) In the revised proposition, the selected subgroups of patients represent a group with a significant clinical unmet need. It is therefore not surprising that the annual exacerbation rates in this population are greater than in the all-adult population. It is considered that in UK clinical practice, outside of the constraints of a RCT setting, these uncontrolled patients may experience higher rates of exacerbation and so thereby the model reflects a conservative valuation of inhaled mannitol to reduce the clinical and economic impact of exacerbations.

36	4.19.	".....in the model derived from the Australian BioGrid study that, for a patient without exacerbations, FEV1% predicted declines with time until age 30 years, and then begins to rise, an assumption which the clinical specialists noted to be unrealistic." ; ...."the manufacturer did not consider the effect of treatment with mannitol on body mass index, even though body mass index was a parameter in the model used to estimate FEV1% predicted ";	**Please add: That on an individual basis lung function declines in all CF patients. However, as commonly observed in other international studies of CF cohorts, the emergence of a healthier population dominating within the cohort (evident at the age of 30-35 years onwards) leads to a reduced decline in lung function for the population. The BioGrid data therefore reflects typical patient characteristics expected from a cohort of CF patients when analysing lung function decline by age.** As described above, there is considerable variability in patient characteristics and disease progression within CF. This individual variability is somewhat masked when examining the cohort as a whole. The characteristics of lung function decline by age in the BioGrid cohort of patients would be considered consistent with other data sources that examine a cohort of patients by age. Typically this is characterised by a rapid decline in lung function observed from birth to early teens, whereby an acceleration may occur during adolescence, leading to a stabilisation in the early twenties to mid thirties. At approximately age 30-35 years old onwards, the cohort reflects a plateau or increase in lung function. These characteristics of a lung function decline by age are consistent with other reported cohorts in other countries including the UK (UK CF Trust Registry Report, 2010), USA (Liou *et al.,* 2012) as well as the broader Australian population in their CF Trust Registry. In examining this curve on an individual patient basis, one sees that the inflection of an improved lung function, is in part, likely a consequence of healthier patients out-surviving their counter-parts with a poorer prognosis. Consequently, on a cohort basis, an emergent healthier patient population starts to dominate the curve at age 30-35 years to appear to show an improvement in lung function for the cohort, although on an individual basis these 'healthier' patients still experience a decline in lung function (albeit at a lower rate) . Please see Appendix for visual comparability of lung function decline by age in CF patient cohorts from BioGrid, UK, Australian and US registry datasets. **Please re-state: BMI was not a significant variable in the regression analysis and so was not included as a covariant:** Regression models were derived from relevant populations within the BioGrid dataset. In all cases, variables were tested for their significance to influence the regression model. Only statistically significant influential variables were used as covariates in the construction of the regression model. The exclusion of BMI was due to non-significance of this variable within the cohort analysed. In the updated model for non-users with the 0% continuation rule, BMI is no longer significant in the prediction of FEV% predicted at 26 weeks. On page 183 of the MS, sensitivity of the CUA was conducted to test the influence of BMI on the ICER. At the levels tested, BMI was also found to have only a limited impact on the ICER results. Specifically, sensitivity to baseline BMI variance (tested at minimum and maximum seen in the pooled adult data) and to the extremes in variation observed from using the Cholesky decomposition method for BMI used to predict the FEV1 % predicted after 26 weeks of treatment, demonstrated a small impact on ICER results.

		" The Committee was concerned that the search strategy employed by the manufacturer in constructing the model may have excluded relevant UK data which would have more accurately informed estimates of pulmonary function and mortality."	As detailed on pages 142-7 of the MS, an all cause mortality rate was estimated from UK life tables from the UK Actuaries Department, based upon the gender distribution from the trial and age specific (data not shown to conserve space, but available in the model). Since, CF patients have a lower life expectancy than the general community, survival was linked to lung function and a number of factors including BMI and specific respiratory infections. Since there is reasonable similarity in treatment practices between the UK and Australia and that the BioGrid patient characteristics within the dataset were comparable to those observed in the typical UK populations (UK CF Trust Registry Report, 2010: see Section summary above), BioGrid data (as the best available data source at the time) was used to explore predictors of mortality. A Cox's proportional hazard survival model for CF survival from birth to CF-related death was developed for this purpose. Since FEV1 was the primary outcome of the mannitol pivotal trials particular focus was on the relationship between FEV1 and survival. Other potential risk factors, like gender and BMI were also investigated and presented within the MS (BioGrid survival analyses: Note that FEV1 % predicted and BMI were included as time varying covariates in the model). The results showed consistency with other published UK and international studies derived from a systematic search review of the published literature at the time. These results are also consistent with that presented by Dodge et al., 2007 of UK survival of CF patients over time. **CF patient mortality by age (UK population vs. derived using BioGrid)**  Mortality observed In a UK population (Dodge, 2007) is comparable to that derived from the BioGrid dataset (as provided in the MS)

PROPOSED ELIGIBILITY CRITERIA AND STOPPING RULES		
		As a consequence of poorly effective historical precedents, we understand the Committee's concerns with introducing treatment stopping rules based on FEV1 criteria. In the past, stopping rules have been applied to the continuation of rhDNase treatment. Although some centres still operate a FEV1 threshold stopping rule for rhDNase (In an independently conducted survey, 14 out of 29 adult CF clinicians reported that their centre currently had an agreed stopping rule in place regarding the usage of rhDNase), this has generally fallen into disrepute because of a lack of correlation proven to exist between FEV1 response and reduction in exacerbations, for patients treated with rhDNase. As described above (in comments to Section 3.35), whilst on a population basis FEV1 has been shown to correlate with exacerbation risk, on a patient-level basis physicians look to provide treatment on an individual basis, and so have grown increasingly reluctant to stop treatment with rhDNase in patients who have not reached the FEV1 improvement threshold due to a lack of evidence of correlation with exacerbations, and in the hope they will still be getting a benefit in reduced exacerbations. In other cases, continuation of rhDNase in uncontrolled patients may also reflect the absence of alternative more effective options (See Patient Treatment Pathway section below). In the case of inhaled mannitol, trial data clearly shows that a FEV1 response to inhaled mannitol at 6 weeks is a very sensitive and specific predictor of response at 26 weeks. In addition, patients demonstrating any improvement in FEV1 over the 26 weeks of the study had 59% fewer exacerbations than those that experienced a decline in lung function. A stopping rule based on FEV1 improvement at 6 weeks is therefore clinically validated as a predictor of continued response at 26 weeks and reduced exacerbations, for patients receiving inhaled mannitol. A stopping rule is also appropriate to improve the cost-effectiveness of a treatment (i.e. by providing a treatment only to those patients that may receive a benefit from it), as well as for physicians and patients (encumbered with a heavy treatment burden) to rationally remove medicines that are not effective from their regimen. Inhaled mannitol also provides a new option for patients currently uncontrolled on rhDNase. In agreement with the Committee's perspective (Section 4.4 of the ACD), there is an accepted need for a range of treatment options in CF and that inhaled mannitol could help ease the burden of the disease. Given the need to find treatments for patients with limited options, mannitol represents a new option for patients that are uncontrolled on their current treatment. This view is shared by 62 European CF specialist clinicians in a consensus statement, including 12 physicians from the UK (Appendix: Consensus statement supporting a need for Bronchitol and provided to the EMA). As also acknowledged by the Committee (in Section 4.2 of the ACD), the patient treatment pathway in CF is complex (see Patient Treatment Pathway section below). Treatment therefore requires individual tailoring to the patients needs and as such 98% of CF patients are treated in registered CF centres, under specialist clinician care. The combination of treatment being controlled by CF specialists, within a limited number of centres that represent the majority of patients in the UK, again lends itself extremely well to appropriate specialist and contained prescribing of inhaled mannitol to only those patients that experience a benefit. The small number of Adult CF centres in England and Wales (n=19) also lends itself to an implementable mechanism to manage compliance of a stopping rule. So at a time when patients are looking for more effective medications but also not to increase their treatment burden a stopping rule based on FEV1 response at 6 weeks is practical, scientifically rational, likely to be adhered to and is easily monitored. A view that has received clinical endorsement from the CF community.

12	3.21	"The model includes a discontinuation rule under which patients who do not respond to mannitol treatment within 6 weeks stop mannitol and switch to best standard of care."	**In acknowledging the concerns of the committee, please give consideration to a revised proposition of using a 0% improvement stopping rule at 6 week, to alleviate concerns of adherence:** In addition the outlined scientific and clinical rationale of an implementable stopping rule that can be effectively managed by the CF community, a revised stopping rule is proposed by the Manufacturer. In acknowledging the Committee's concerns, a 0% improvement stopping rule is proposed (and modelled) in order to discontinue inhaled mannitol for patients at 6 weeks, if no benefit from treatment is received. In listening to the views of the CF community, it is expected that by lowering this threshold of response needed to continue treatment, clinicians will be able to implement the rule more easily given the inherent variability in measuring lung function on a day-to-day basis. In the CUA, modifying the stopping criteria from a 5% improvement in FEV1 (absolute or % predicted) and/or 100ml increase, to a 0% improvement has increased the ICER from £19,550/QALY to £19,993/ QALY in the base case. However, this trade-off is accepted by the manufacturer in the interest of enabling an easier method for clinicians and patients to judge the benefits of treatment, employing a rule that still retains a high degree of specificity and sensitivity in predicting response at 26 weeks, and facilitates a mechanism of control by NHS budget-holders.
29	4.8.	".....The Committee heard from clinical specialists that both absolute FEV1 and FEV1% predicted measurements are used in clinical practice, that between 75 and 100 ml absolute FEV1 change is clinically meaningful, and that FEV1% predicted is used for children and to compare adult patients with their peers. The Committee noted that in the trials patients who did not meet the definition of response stopped treatment at 6 weeks. The clinical specialist explained that this differed from clinical practice in the UK. If a patient felt better, but did not reach the threshold defining response (for example, their absolute FEV1 increased by only 80 ml), the clinician would be unlikely to recommend stopping treatment. The patient expert concurred, stating that FEV1% predicted can vary from day to day, and that small changes could make a difference to daily life and activity. The Committee concluded that the FEV1 response outcomes were clinically relevant, but was not convinced that clinicians and patients would adhere to the stopping criteria assumed within the manufacturer's submission."	
37	4.22.	"The Committee also considered the effect of the stopping rule, having heard from the clinical specialist that clinicians and patients would be unlikely to follow the trials' stopping rule in clinical practice. The Committee concluded that the model did not adequately reflect adherence to treatment and to stopping rules, and that the ICERs were likely to be higher if the model reflected clinical practice."	**In acknowledging the concerns of the committee, please give consideration to the revised proposition of using a 0% improvement stopping rule at 6 week):** In addition to the context outlined above and the proposed 0% improvement at 6 weeks stopping rule, sensitivity analysis within the model has been applied to evaluate the impact of treatment discontinuation. Please see analysis report provided for tornado diagram and sensitivity analysis. We have implemented a stopping rule based on dropouts observed in the open-label phase. The sensitivity analysis shows the results are not sensitive to this parameter.
41	4.30.	"The Committee considered the subgroup defined by baseline FEV1% predicted of <40 in the rhDNase ineligible subgroup. The ICER for this subgroup was the only one presented by the manufacturer which was less than £30,000 per QALY."	**PLEASE CORRECT:** In addition to the FEV1% predicted of <40 in the rhDNase ineligible subgroup ICER (£23,704/ QALY) in the initial MS (and as requested in the NICE Scoping document), please clarify that in subsequent clarification responses by the Manufacturer others were presented including rhDNase non-user, unsuitable patients with an all adult exacerbation rate applied (£27,673/QALY), and with a exacerbation rate derived from the rhDNase non-user, unsuitable population (£19,828/QALY). Many others were close to a £30,000/QALY threshold . **Please note, that in the revised proposition to NICE, a base case CUA reflects ICERs <£20K per QALY, with sensitivity and scenario analysis showing further decreases in the ICER. Please see accompanying report and analysis.**

PATIENT TREATMENT PATHWAY & SUBGROUPS RELEVANT TO PATIENTS WITH CYSTIC FIBROSIS IN THE UK		
		As also acknowledged by the Committee (in Section 4.2 of the ACD), the patient treatment pathway in CF is complex. Given the heterogeneous nature of the disease as a consequence of the intrinsic variability in patients (due to underlying genetic and phenotypic expression of the disease), overlayed by extrinsic influences on disease progression (e.g. exposure to infection and treatment adherence) a patient's disease progression is highly variable, and therefore so is the treatment pathway. Treatment requires individual tailoring to the patients needs and clinical guidelines reflect an individualised approach to treatment protocols (www.mapofmedicine.com Management of Adult patients; Complications). Whilst 98% of CF patients are treated in registered CF centres, under specialist clinician care, the treatments prescribed are not captured or available in the UK public record with sufficient granularity to be able to derive sufficient insight upon which to evaluate a patient treatment pathway. To be able to provide an insight to NICE of the current treatment practices for adult CF patients in England and Wales, an independently conducted survey was commissioned by Pharmaxis (June 2012). Specifically, the survey examined rhDNase and hyprertonic saline usage; treatment satisfaction; and how physicians would use inhaled mannitol (Bronchitol®) based in their current case mix. The survey captured data from 29 CF respiratory physicians (17 Consultant Physicians and 11 Senior Registrars) across at least 10 of the 19 specialist adult CF centres in England and Wales. Together they reported that they were responsible for 4,147 patients of which 4,002 were adults representing a substantial proportion of the adult patients within the England and Wales. Summary results are provided below with full details of the survey provided in the Appendices. • The results of the survey clearly demonstrate that most patients in UK CF adult centres have already been trialled on the existing airway clearance drugs. Only 18% of patients have never used rhDNase or hypertonic saline and consequently the opportunity for inhaled mannitol to be used as a first line agent is very small. • Hypertonic saline usage is fairly common in CF adults, but its usage at a dose that has been proven to reduce exacerbations in an RCT (4ml, 7% twice daily) is low. No qualitative information was collected in the survey to find out why hypertonic saline is chronically under dosed but the comments from the clinician and patient during the first NICE appraisal meeting suggest that poor tolerability is a key factor. • About one third of patients are perceived by clinicians to be uncontrolled irrespective of the treatment they are taking. This underlines the level of unmet need which exists in the adult CF population despite the widespread use of existing treatments • Clinicians see inhaled mannitol as a potentially useful treatment particularly in patients who are not well controlled despite treatment with hypertonic saline and/or rhDNase (50% of the proposed population), and a beneficial option for patients not currently receiving treatment (19%). • Extrapolating these results to the CF population in the UK the proposed Bronchitol-treated population would be 1,000 patients. The acquisition cost for Bronchitol in year-1 would be estimated as ~ £1.2M rising to £3.3M in year-5, assuming 20% of these patients would be treated in year 1 and 55% would be treated in year-5. (see Comments relating to Section 5.0 below). • This compares with the 4,000 patients currently estimated to be on rhDNase (UK CF Trust Registry Report and IMS data) and the 3,600 patients estimated to be on hypertonic saline based on extrapolations from the survey. • Inhaled mannitol was not perceived as a treatment that will replace existing treatments on a significant scale when those patients are well controlled. • The % of patients on hypertonic saline who are well controlled that would be considered for a trial on inhaled mannitol is very low (11%).

42	4.31.	Section 4.31: "The Committee concluded that treatment with an inhaler provided practical advantages over treatment with nebulisers, but because mannitol as an add-on therapy would not replace the use of nebulisers, and so could not be considered a step change in treatment.	**Please revise statement recognising the advancement in CF treatment (step change) that inhaled mannitol provides through reducing exacerbations and improving lung function in population experiencing a progressive decline in lung function.** Whilst The manufacturer agrees that Bronchitol® has been innovated to provide a solution for CF patients that lends itself to convenience through its formulation and disposable device to reduce a need to routinely clean nebulisers multiple times a day to avoid microbial inhalation, as well as avoid the routine maintenance and replacement of nebulisers. This statement in the preliminary ACD significantly undervalues the innovation to CF patient treatment. Inhaled mannitol represents a true step change in CF treatment not only in that its formulation has adherence benefits but more importantly in treatment outcomes. The current median age of death from CF in the UK is less than 30 years of age and there is an undeniable need for new treatments. The only approved treatment for airway clearance in CF is rhDNase and that has been available since 1994. Independent survey data (see Patient Treatment Pathway section above) from at least 10 of the 19 adult centres in England and Wales confirms that 28%and 58% of adult patients have trialled rhDNase with or without hypertonic saline (respectively, note patients may have tried both and so may represent double-counting). Of the 22% and 43% of patients currently taking rhDNase with or without hypertonic 30% and 33% of patients are inadequately controlled. It is also reasonable to assume that many of the patients currently not taking rhDNase are now not using it because of poor efficacy, tolerability, compliance and /or adverse responses. Mannitol has a different mechanism of action to rhDNase and has been shown to improve lung function and reduce exacerbations when used in addition to rhDNase and in those patients who have already tried it and no longer use it as well as in patients naive to rhDNase. There is also evidence from a cross-over study in children that patients who do not respond to rhDNase do respond to mannitol (Bush *et al.,* 2007). It is undeniable therefore that for CF patients, mannitol represents a step change in treatment efficacy when compared to rhDNase. The other comparator in the NICE scoping document, hypertonic saline, has a mode of action similar but not identical to mannitol. It is used in only approximately 40% of patients (Agent et al., 2012) and this was confirmed in the patient treatment pathway survey (41%) and in a large percentage of these the dose taken is significantly less than that used in the one long term study of hypertonic saline (Elkins, 2006). There is no evidence that hypertonic saline can produce a long term benefit in lung function (Wark and McDonald, 2009) as demonstrated for mannitol and the reduction in exacerbations produced in this one study was in a population that had higher levels of pseudomonas (see comments relating to Section 3.36) and yet far lower use of antibiotics than is seen in the UK CF population (UK CF Trust Registry Report, 2010). Conversely Mannitol has a proven efficacy and safety profile in a patient population similar to that found in UK clinics and had high levels of compliance in the clinical studies with more than 80% of patients at the end of the double blind phase of the trial choosing to enter an open label extension of the study. It is therefore clear that mannitol represents a step change in treatment compared to hypertonic saline from an efficacy, safety and adherence perspective.
27	4.5.	"The Committee noted that the manufacturer did not explain for whom rhDNase was unsuitable, specifically those who were ineligible, intolerant, or inadequately responsive to rhDNase. The clinical specialist explained that those ineligible to take rhDNase were those not fulfilling the eligibility criteria for treatment with mannitol within the trials."	**Please provide clarification as detailed on unsuitable rhDNase users.** The manufacturer recorded reasons why patients were not taking rhDNase on entry to CF301, however it was recorded retrospectively. This data was collected prospectively in CF-302. All patients who were not using rhDNase were asked if they had ever used rhDNase, and if so, why were they not using it currently. The reasons were categorised as ineligible, intolerant, or inadequately responsive to rhDNase. If another reason was given for not currently taking rhDNase (eg. The patient could not afford it) then the patient was not included in those groups. Please see the Patient Treatment Pathway section above for further details of rhDNase usage in current clinical practice.

REVISED COST-UTILITY ANLYSIS & PROPOSITION

As highlighted above, to reflect the comments received by NICE and the needs of the CF community, the manufacturer has identified two CF patient populations who have the most unmet medical need and in which inhaled mannitol provides a significant clinical benefit.

- **Patients receiving Best Supportive Care (BSC) without add-on rhDNase.**
- **Patients receiving BSC (+/- rhDNase) experiencing a greater than 2% decline in FEV1 percent predicted per year.**

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. To assess the clinical and economic impact of these propositions, the CUA has been revised as follows:

- To reflect the two base cases from the revised proposition (above) and the change in the stopping rule.
- The CUA model was updated in line with comments received from the ERG and NICE. (Details of the revision are provided below and within the analysis reports attached).
- To address concerns raised by the ERG and NICE, additional sensitivity and scenarios analysis have been modelled to examine:
    - the impact of key clinical and economic influences on the model,
    - the duration of treatment effect,
    - drop-out rates (further details are provided in the attached analysis report and model)

The analysis shows that:

- **In adult rhDNase non-users, adding Bronchitol to BSC is cost-effective with an ICER of £19,993/QALY.**
- In the PSA, the probability of the ICER being below a WTP threshold of £30,000 was 82.2%, and in lowering the WTP threshold to £20,000, the probability was 46.5%, both of which represent reasonable levels of cost-effectiveness on a population basis.
- In sensitivity analysis, the results remained robust, with greatest variance on the ICER result being the treatment effect associate with Bronchitol. Since the base case has taken a conservative approach wherever choices have needed to be made, the result of this variation was generally to reduce the ICER results.
- Consistent with the clinical unmet needs of the CF community in England Wales, Bronchitol represents a cost-effective option for patients receiving Best Supportive Care, without add-on rhDNase

- **In adult patients with >2% FEV1% predicted decline per year, adding Bronchitol to BSC is reasonably cost-effective with an ICER of £36,214/QALY**.
- In the PSA, the probability of the ICER being below a WTP threshold of £30,000 was 20.8%. In lowering the WTP threshold to £20,000, the probability was 1.2%. Whilst representing borderline thresholds of acceptability, it is important to recognise that the patients in this analysis have been derived from a sequentially reduced dataset and that patients with CF experience large variability in their individualised disease progression and treatment pathway (see Executive Summary to the responses). In focusing on this specific sub-population it is also recognised that these patients experience the most rapid decline in lung function and experience the highest exacerbation rates. Their clinical course is therefore even more variable. In providing an option for these patients, enables a significantly unmet need for CF patients to be addressed with a new treatment option.
- In sensitivity analysis, the results remained relatively robust, with greatest variance on the ICER results being related to the starting FEV1, treatment effect associate with Bronchitol, and disutility associated with exacerbation. To a large extent these variance reflect the inherent variability of patients in need of a new treatment option.
- Consistent with the clinical unmet needs of the CF community in England Wales, Bronchitol provides a potentially cost-effective option for patients receiving BSC (with or without rhDNase) that experience the greatest decline in lung function - a population with the most significant unmet need.

40	4.27.	"The Committee concluded that the ERG modelling incorporating health state specific costs was more appropriate."	**Please note: In acknowledging the ERG comments the manufacturer has revised the base case in the CUA to incorporate this change in the revised proposition** (Please see analysis report provided in appendices).
15	3.27	"The manufacturer also performed sensitivity analyses showing the effect of treatment failure after 1, 5, 10 and 20 years….If the improvement in FEV1% predicted were maintained for 1 year the ICER was £149,587 per QALY gained; if improvements were maintained for 5, 10 and 20 years, the ICERs were £86,981, £63,539 and £49,907 per QALY gained respectively."	**Please note: In acknowledging the ERG comments the manufacturer has revised the base case in the CUA to incorporate this change in the revised proposition.** The manufacturer has specifically examined the duration of a treatment effect and its influence on the ICER outcomes. Based on the two extension trials of DPM-CF-301 and DPM-CF-302 (pg 91 of the MS and published by Bilton *et al.*, 2011; Aitken *et al*., 2011; Burness *et al.,* 2012), a clear treatment benefit is observed as being maintained to 78 weeks for patients treated with mannitol. Furthermore, in control patients switched to mannitol a significant improvement in lung function is observed to similar levels of the original mannitol treated population. Therefore, it is reasonable to assume that patients receiving mannitol and responding to treatment after 6 weeks are likely to retain their treatment benefit to at least 78 weeks. In the base case analysis, an assumption of maintained treatment affect to 74 weeks was taken due to the cycle length being 12 weeks. The outcomes at 26 weeks were carried forward for the next 4 cycles in the model (48 weeks) unless the patient died. In addition to a maintained treatment benefit to 74 weeks, the model incorporated a drop-out of patients over time. This drop-out rate was calculated based on the average of that observed over the 14-78 weeks of the pooled trials, with the population adjusted for depending on a prior removal of patients according to the responder stopping rule applied at 6 weeks. Sensitivity of the base case analysis to the drop-out rate was also conducted. In additional scenario analysis, the duration of maintained treatment effect beyond 78 weeks has been examined by carrying forward the maintained benefits to 8 cycles (8*12weeks), before following a parallel decline in FEV1 % predicted to the control arm. **(please see summary section: REVISED COST-UTILITY ANLYSIS & PROPOSITION)**
22	3.47.	"The ERG examined the assumption that the FEV1% predicted improvement caused by mannitol would be maintained over the lifetime of the patient by reducing the time horizon of the model as a proxy for a shorter duration of effectiveness. This was similar to the scenario analysis conducted by the manufacturer. The ERG's analyses resulted in ICERs for a time horizon of 5 years of £188,551 per QALY gained for rhDNase users, and £90,126 per QALY gained for those ineligible for rhDNase. For a time horizon of 10 years, the corresponding ICERs were £127,625 and £49,854 per QALY gained respectively. "	
36	4.21	"The Committee noted that the assumption of a maintained long term benefit of mannitol would affect the ICER favourably, but that there was significant uncertainty around this assumption and the manufacturer had not explored the effect of tapering of benefit through sensitivity analyses."	
17	3.31	"For FEV1% predicted of 60–79%, the ICERs were £51,049 and £45,247 per QALY gained for rhDNase users and non-users respectively. For FEV1% predicted 40-59%, the ICERs were £45,630 and £39,511 per QALY gained for rhDNaser users and non-users, respectively. For FEV1% predicted < 40%, corresponding ICERs were £30,746 and£23,704 per QALY gained respectively."	**Please note: In acknowledging the ERG comments the manufacturer has revised the base case in the CUA to incorporate these suggestions and observations in the revised proposition (please see summary section: REVISED COST-UTILITY ANLYSIS & PROPOSITION).**
20	3.37.	"The ERG deemed the structure of the model sufficiently inclusive and diverse to model the complexities of cystic fibrosis, but the ERG expressed some concerns about the cost-effectiveness model."	
20	3.39.	ERG found small mistakes in the model, but noted that the validation checks matched the clinical trial results at 26 weeks.	

21	3.43.	"However, because of a lack of data, the ERG could not investigate the manufacturer's assumption that the probability of moving between health states remained the same over the lifetime of the patient."	
21	3.42.	"The ERG was concerned about the assumption made by the manufacturer that HUI2 utility and cost parameters depended on treatment, but not on health state."	
34	4.16.	"The Committee noted that the structure of the model was not a health state model, but rather was a model of the cystic fibrosis treatment pathway. The Committee was aware of the ERG's concerns about the manufacturer's assumptions that any improvement in FEV1% predicted would be maintained throughout the lifetime of the patient, and that it would be directly translated into lowered morbidity and mortality rates, as well as the assumption that HUI2 utility and cost parameters depended on treatment, and not on health state. The Committee concluded that the cost-effectiveness model was complex and may not adequately reflect the clinical trial data."	
21	3.40.	"The ERG noted that one of the most important assumptions made by the manufacturer was that any improvement in FEV1% predicted would be maintained throughout the lifetime of the patient, and would directly translate into lower rates of morbidity and mortality. The ERG was concerned that there were no long-term data to support this assumption. "	**Please note that as described above, patients have been shown to experience a sustained benefit to at least 78 weeks of treatment with inhaled mannitol** Whilst this duration is too short to evaluate any survival advantage, there is strong evidence that a patient's FEV1 is linked to mortality. This is supported by the analyses in the BioGrid data.
23	3.48.	"The ERG calculated that patients with improved respiratory symptoms have 93% of the overall costs, whereas those without improved symptoms have 105% of the overall costs. The ERG assumed these percentages also applied to rhDNase mean costs. The ERG did not provide separate ICERs using these differential costs, but derived estimated 6-month treatment costs for improved and not improved respiratory symptoms in rhDNase users and ineligible non-users. The ERG concluded that health state-specific costs should be used rather than treatment-specific costs."	**Please note that in the revise model we have used actual patient level data to derive these costs that the ERG did not have access too**
40	4.28.	"The Committee concluded that the ICERs for mannitol were unlikely to fall below £30,000 per QALY gained."	**Please note, that in the revised proposition to NICE, the base case CUA reflects ICERs <£30K per QALY, with sensitivity and scenario analysis showing further decreases in the ICER. Please see accompanying report and analysis.**

<table>
<tr>
<td>49</td>
<td>5.00</td>
<td>Implementation (see also MS submission) - Budget impact assessment</td>
<td>The estimated acquisition cost for Bronchitol in year-1 would be estimated as ~ £1.2M rising to £3.3M in year-5:
<table>
<tr><th></th><th>Est. % market share</th><th>Est. No. receiving Bronchitol</th><th>Est cost of treatment acquisition</th><th>Cumulative cost of treatment acquisition</th></tr>
<tr><td>Year 1</td><td>20</td><td>200</td><td>£ 1.205 M</td><td>£ 1.205 M</td></tr>
<tr><td>Year 2</td><td>30</td><td>300</td><td>£ 1.807 M</td><td>£ 3.012 M</td></tr>
<tr><td>Year 3</td><td>40</td><td>400</td><td>£ 2.410 M</td><td>£ 5.422 M</td></tr>
<tr><td>Year 4</td><td>50</td><td>500</td><td>£ 3.012 M</td><td>£ 8.434 M</td></tr>
<tr><td>Year 5</td><td>55</td><td>550</td><td>£ 3.313 M</td><td>£ 11.747 M</td></tr>
</table>

Total population eligible for Bronchitol = 1000 (Patient Treatment Pathway survey)
The cost of Bronchitol acquisition have assumed all patients receive treatment at the beginning of the year
Cost represents acquisition only, and no further adjustments have been made, for example reflecting: patient survival, non-continuation of treatment for patients that respond to treatment at 6 weeks (based on a 0% improvement in lung function); natural drop-out rates or effectiveness incorporated within the costs of treatment (including background treatment with antibiotics and other medical resource utilisation as described in the CUA

.</td>
</tr>
</table>

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APPENDICIES

APPENDIX I: Supplementary data to support responses

FEV_1 responders in adults per rhDNase use

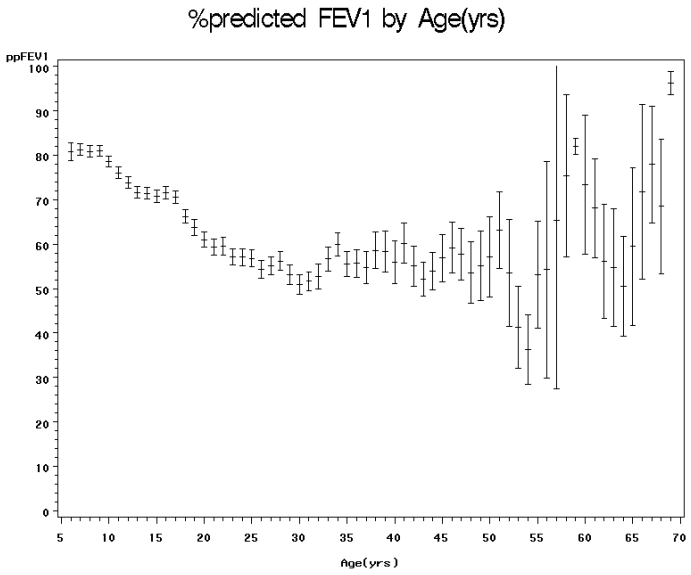
	DPM-CF-301		DPM-CF-302		Pooled	
	Mannitol n/N (%)	Control n/N (%)	Mannitol n/N (%)	Control n/N (%)	Mannitol n/N (%)	Control n/N (%)
Adults						
Baseline to Week 26						
FEV_1 ≥100 mL	37/114 (32.5%)	15/76 (19.7%)	35/93 (37.6%)	15/58 (25.9%)	72/207 (34.8%)	30/134 (22.4%)
FEV_1 ≥5%	37/114 (32.5%)	16/76 (21.1%)	31/93 (33.3%)	14/58 (24.1%)	68/207 (32.9%)	30/134 (22.4%)
% pred. FEV_1 ≥5%	**26/114 (22.8%)**	**8/79 n(10.5%)**	22/93 (23.7%)	11/58 (19.0%)	48/207 (23.2%)	19/134 (14.2%)
Baseline to Week 6						
Combined Responder at week 6*	58/114 (50.9%)	25/76 (32.9%)	42/93 (45.2%)	21/58 (36.2%)	100/207 (48.3%)	46/134 (34.3%)
Adults DNase users						
Baseline to Week 26						
FEV_1 ≥100 mL	16/58 (27.6%)	3/44 (6.8%)	25/64 (39.1%)	9/41 (22.0%)	41/122 (33.6%)	12/85 (14.1%)
FEV_1 ≥5%	16/58 (27.6%)	3/44 (6.8%)	23/64 (35.9%)	9/41 (22.0%)	39/122 (32.0%)	12/85 (14.1%)
% pred. FEV_1 ≥5%	11/58 (19.0%)	1/44 (2.3%)	16/64 (25.0%)	7/41 (17.1%)	27/122 (22.1%)	8/85 (9.4%)
Baseline to Week 6						
Combined Responder at week 6*	24/58 (41.4%)	12/44 (27.3%)	29/64 (45.3%)	16/41 (39.0%)	**53/122 (43%)**	**28/85 (33%)**
Adults non DNase users						
Baseline to Week 26						
FEV_1 ≥100 mL	21/56 (37.5%)	12/32 (37.5%)	10/29 (34.5%)	6/17 (35.3%)	31/85 (36.5%)	18/49 (36.7%)
FEV_1 ≥5%	21/56 (37.5%)	13/32 (40.6%)	8/29 (27.6%)	5/17 (29.4%)	29/85 (34.1%)	18/49 (36.7%)
% pred. FEV_1 ≥5%	15/56 (26.8%)	7/32 (21.9%)	6/29 (20.7%)	4/17 (23.5%)	21/85 (24.7%)	11/49 (22.4%)
Baseline to Week 6						
Combined Responder at week 6*	34/56 (60.7%)	13/32 (40.6%)	13/29 (44.8%)	5/17 (44.8%)	**47/85 (55%)**	**18/59 (37%)**

*Relative increase in at least 5% or an absolute increase of at least 100 mL in the FEV_1 at week 6 from baseline

Comparability of age versus lung function decline in international cohort analyses of CF patients with BioGrid data

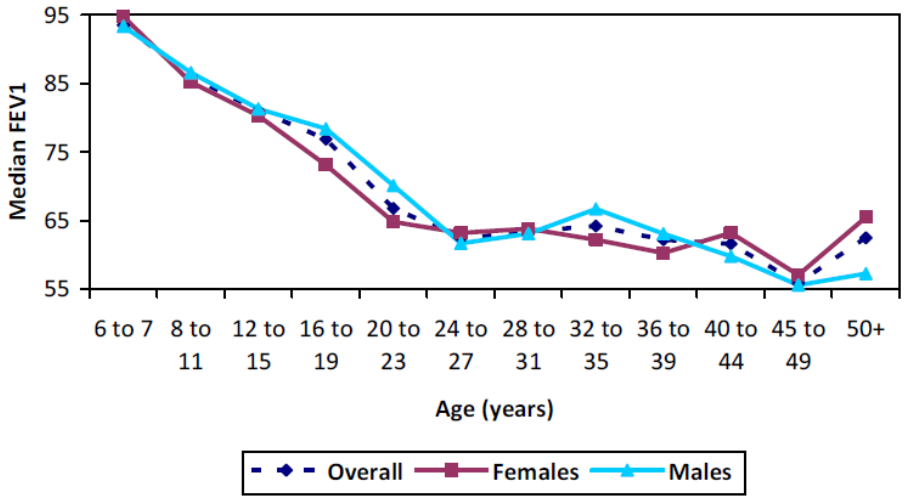
Please note: evidence of an emergent healthier and surviving population appearing to improve lung function at 30-35 years and older as consistent feature of all cohorts.

BioGrid cohort (Previously provided in the appendix of the MS)

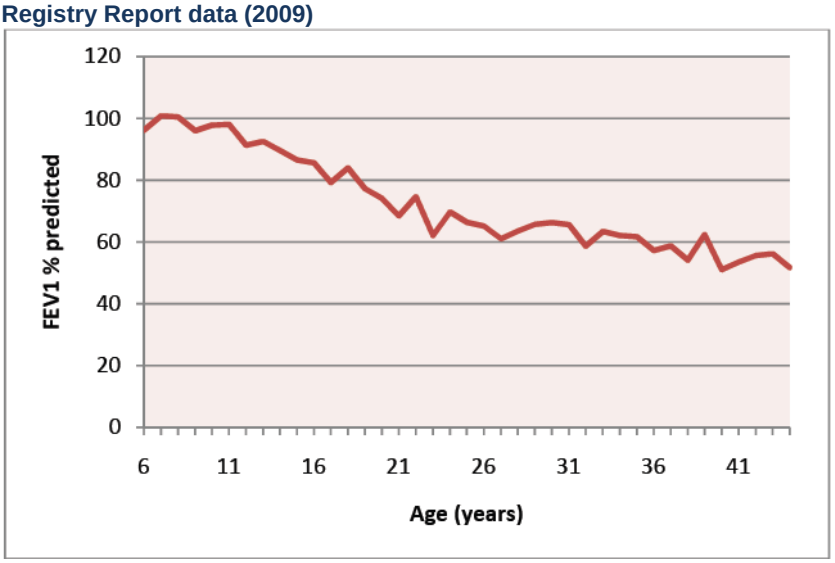


UK CF Trust Registry Report data (2010)

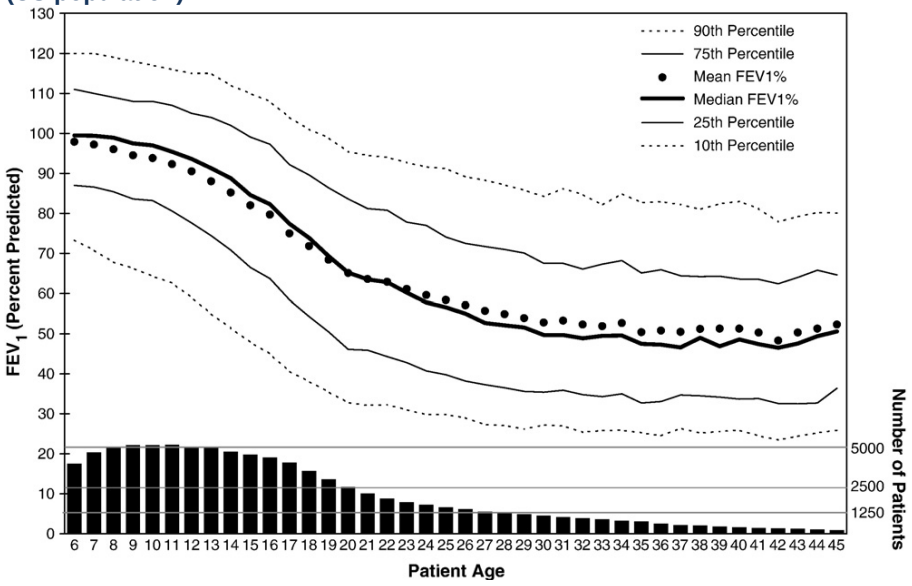
1.14 Median FEV_1 (% predicted) among patients aged 6 years and older (n=6120)



Australian CF Trust Registry Report data (2009)



Liou *et al.*, 2010 (US population)



APPENDIX II – Supporting analysis (provided electronically)

Patient Treatment Pathway analysis report (PDF)

Cost-utility analysis report and model in TreeAge

APPENDIX III – supporting references (provided electronically)

- Clinical Trial protocols for DPM-CF-301 and DPM-CF-302
- UK CF Trust Annual Registry Report 2010: www.cftrust.org.uk/aboutcf/publications/cfregistryreports/
- Australian CF Trust Annual Registry Report (2009): www.cysticfibrosis.org.au/projects/dataregistry/
- Minutes from the Scientific Advisory Group (SAG) Meeting – confidential information removed
- Dentice et al., Definitions used for Pulmonary Exacerbation in Clinical Trials in Cystic Fibrosis (CF): a Systematic Review and Meta-analysis, European Cystic Fibrosis meeting (Dublin) June 2012)
- Consensus statement supporting a need for inhaled mannitol (Bronchitol®) provided to the EMA
- Bilton et al., 301 OLP for 12 months 2010
- Aitken et al., 302 OLP for 6 months 2011

Clinical Study Protocol DPM-CF-301

Version 5.1, July 23, 2009

Long Term Administration of Inhaled Dry Powder Mannitol In Cystic Fibrosis – A Safety and Efficacy Study §

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SYNOPSIS

Title*:* Long Term Administration of Inhaled Dry Powder Mannitol in Cystic Fibrosis – A Safety and Efficacy Study

Sponsor: Pharmaxis Limited, 20 Rodborough Road, Frenchs Forest, NSW 2086 Australia.

Primary objective

- To determine the effect of IDPM compared to control on FEV_1 in patients with CF

Secondary Objectives

- To determine the effect of IDPM compared to control on FEV_1 in patients with CF on existing RhDNase treatment. (key objective)

To assess whether IDPM treatment:

- Reduces pulmonary exacerbations in those taking RhDNase as a sub-group and in the total cohort (key objective)
- Improves quality of life (key objective)
- Reduces days on IV antibiotics, rescue oral or inhaled antibiotics
- Reduces days in hospital due to pulmonary exacerbations
- Improves other measures of lung function
- Demonstrates an appropriate safety profile (adverse events, haematology, biochemistry, change in bronchodilator response, sputum microbiology, physical examination)
- Reduces hospital and community care costs

No. of Subjects: Minimum 340 subjects to be randomised

Period of enrolment*:* 18 months

Number of subject visits: 5 (plus 2 each in 2 open label phases)

Duration of study treatment: 26 weeks (plus 26 weeks each in 2 open label phases)

Study design: Randomised, controlled, parallel arm, double blind

Study population: Cystic fibrosis, aged $\geq$6 years, baseline FEV_1 $\geq$30% and <90% predicted, not pregnant or breast feeding, no intolerance to mannitol or beta agonists, no concurrent use of hypertonic saline or beta blockers for the study duration.

Name of study drug*:* Dry powder mannitol for inhalation (IDPM)

Dose and administration rate: 400 mg BD or control BD in a 3:2 randomisation ratio

Blinding: Double blinded

Indication: Cystic Fibrosis

Drug Administration*:* Inhalation via dry powder inhaler

Primary Endpoint: Change in absolute FEV_1

Secondary Endpoints:

- Change in absolute FEV_1(RhDNase group)
- Pulmonary exacerbations in those taking RhDNase as a sub-group and in the total cohort
- Quality of Life Scores using Cystic Fibrosis Questionnaire
- Rescue antibiotic use (number of agents, course and days of use)
- Change in FVC, FEF_{25-75} from baseline
- Days in hospital due to pulmonary exacerbations
- Cost effectiveness including total costs of hospital and community care
- Safety

TABLE OF CONTENTS

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LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
ATS	American Thoracic Society
BD	Twice a Day
BHR	Bronchial Hyperresponsiveness
BMI	Body Mass Index
BP	Blood Pressure
BTPS	Body Temperature Pressure Saturation
eCRF	Electronic Case Report Form
DPI	Dry Powder Inhaler
ERS	European Respiratory Society
FEF_{25-75}	Measure Of Small Airway Limitation
FEV_1	Forced Expiratory Volume In Second
FEV_1/FVC	Index Of Airflow Limitation
FOT	Forced Oscillation Technique
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HR	Heart Rate
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IDPM	Inhaled Dry Powder Mannitol
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
ITT	Intention to treat (population)
MRP	Mutual Recognition Procedure
PEF(R)	Peak Expiratory Flow (Rate)
Ph.Eur.	European Pharmacopoeia
PP	Per protocol (population)
PRN	As Required
QOL	Quality Of Life
RDR	Response-Dose Ratio
RhDNase	Recombinant human deoxyribonuclease
RR	Respiratory Rate
RTI	Respiratory Tract Infection.
SAE	Serious Adverse Event
SpO_2	Oxygen Saturation

UNITS OF MEASURE

cm	centimetre
^oC	degrees Celsius
hr	hour
ht	height
kg	kilogram
L	litre
L/min	litres per minute
mg	milligrams
min	minutes
ml	millilitre
mOsmol	milliosmol
sec	second
µg	micrograms
µm	micrometer
w	watts
wt	weight

1 INTRODUCTION AND BACKGROUND INFORMATION

Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder of exocrine glands with a heterozygote frequency of 1 in 20 to 1 in 25 individuals. Cystic fibrosis is the most common lethal genetic disorder affecting Caucasian populations and in spite of genetic counselling, the number of patients with CF is likely to continue to increase for some time as the median survival increases. Prognosis for those with the disease has significantly improved over the past fifty years[1]; the median survival increasing from a few months of life to over 30 years. In the United Kingdom, over a third of patients are now over 15 years of age[2]. The median survival age in the United States was 37 years in 2005.

An understanding of the pathophysiological mechanisms underlying the lung disease in CF is still to be clarified[3-5]. It is thought that the failure of the cystic fibrosis transmembrane regulator (CFTR) results in hyperabsorption of Na+ ions and resorption of fluid from the mucosal to the luminal surface of the lung epithelium. This causes a dehydration of airway secretions with consequent impaction of mucus plaques on cilia and failure of mucus transport up through the bronchi. The lung in CF is characterised by accumulation of thick mucus, chronic bacterial infections and chronic obstructive lung disease. Much of the morbidity and mortality is due to respiratory disease, related to the presence of tenacious sputum, and chronic infection and inflammation. Whether inflammation precedes infection or is an exaggerated consequence of infection is unknown. However by mid childhood, most patients have increased airway secretions, and enhancing mucus clearance with physical techniques (for example active cycle of breathing, positive pressure, and autogenic drainage) is a major goal of therapy.

The mechanism whereby osmotic agents increase clearance of mucus remains unclear. A combination of factors, which include changes in the rheology of mucus favouring ciliary and cough clearance may be responsible. Osmotic agents may change the viscoelastic properties of the mucus by reducing the number of entanglements that mucin polymers form. While ionic agents may achieve this by shielding the fixed charges along the mucin macromolecules, the non-ionic agents may achieve this by disrupting the hydrogen bonds between mucins. Osmotic agents also have the potential to increase the amount of water in the airway lumen. Thus, increased hydration may also contribute to an increase in the transportability of mucus. Additionally, osmotic agents may increase clearance of mucus by stimulating mucus secretion. The effect of osmolarity on mucus secretion could be direct or indirect via release of mediators from epithelial and mast cells and neuropeptides from sensory nerves which are known to be secretagogues. Although an increase in mucus secretion is not seen to be a desirable effect, this stimulation of mucus secretion may help increase clearance of viscous and stagnated mucus. Mannitol may benefit patients by reducing the mucus load acutely, or it may have a prolonged effect on mucociliary clearance. Also, as excessive mucus in the airways may result in some limitation of airflow, a reduction in the mucus load may also improve airway function especially in the small airways.

Infected sputum from patients with CF contains high concentrations of DNA from degenerating

neutrophils. Since purified DNA solutions are known to have high levels of viscoelasticity, the use of RhDNase has been instituted in CF patients and it has been shown to increase FEV_1 by at least 10 – 15% and reduce lung infections in one third to one half of CF patients[6,7]. RhDNase must be considered the "gold standard' mucus clearance agent. However 30-50% of patients do not derive benefit from this treatment. It has previously been shown that hypertonic saline (HS) may also improve bronchial mucus clearance (BMC) in CF patients[8,9], although not all studies do report an improvement in lung function[10]. Inadequate saline induced osmolarity changes due to the dose and use of a jet nebuliser for delivery may account for the lack of HS effect reported[10]. Of note, two weeks of treatment with either hypertonic saline (HS) or RhDNase results in a significant improvement in FEV_1 in subjects with CF [9,11]. One likely mechanism by which the HS works is the creation of an osmotic gradient across the airway epithelium with the consequent movement of water into the airway lumen. This would then improve the biorheology of the secretions and the depth of the periciliary fluid layer leading to the enhanced mucus clearance[12]. It has been shown that HS may improve lung function in some RhDNase failures, but there still remains a hard core who respond to neither treatment[10]. Both RhDNase and HS have to be given using a nebuliser, which is time consuming, inconvenient and unpopular. In addition, RhDNase is limited by its high cost and the requirement for refrigeration. It may be advantageous to have an alternative, non-ionic, dry powder osmotic agent for use in CF.

A formulation of dry powder mannitol, developed by Anderson, Chan and Brannan[13] at the Royal Prince Alfred Hospital Department of Respiratory Medicine, NSW, Australia, is believed to meet the criteria for a suitable agent for use in patients with cystic fibrosis. The osmotic properties of mannitol make it a practical and convenient agent for enhancing mucus clearance from the lungs.

1.1 Name and Description of Investigational Product

D-Mannitol ($C_6H_{14}O_6$ MW 182) is a well known, naturally occurring sugar alcohol found in many vegetables. Mannitol is commonly used as an excipient in pharmaceutical products, and as a food additive. Furthermore, mannitol has been administered orally and intravenously at doses up to 200g for bowel preparation, osmotic diuresis and relief of cerebral oedema. It is a stable substance, and as a powder, has good flow characteristics. Because it resists moisture absorption at high relative humidity, it is a suitable substance to encapsulate for inhalation.

Inhaled dry powder mannitol (IDPM) is prepared in a Therapeutic Goods Administration (TGA) approved facility *(Pharmaxis Limited 2/10 Rodborough Rd Frenchs Forest NSW Australia)* under GMP conditions. Mannitol is dissolved in purified water prior to spray drying, and the water is removed during the manufacturing process. No other component/excipient is included in the formulation. The respirable mannitol powder to be used in this study is prepared by passing a mannitol solution of known concentration through a process of liquid atomization, converted to a fine mist, which is followed by rapid hot air drying. This results in the production of particles that are of respirable size (<7μm in diameter) in sufficient quantity and spherical in shape, which makes them disperse well when aerosolized.

For further details of manufacture and clinical development please refer to the Investigator's Brochure.

1.2 Findings from Clinical Studies

Clinical Pharmacology of Inhaled Dry Powder Mannitol

A study by Daviskas[14], showed that inhalation of dry powder mannitol increased mucociliary clearance. Six healthy subjects and six asthmatics received 3 treatments, each 48 hr apart. At Visit 1, they were assessed for responsiveness of their airways to dry powder mannitol to determine the dose of mannitol for subsequent visits. For asthmatic subjects, a mean dose of 267 mg mannitol produced a mean decrease in FEV_1 of 22% and a mean of 13 coughs. For non-asthmatic subjects, 400 mg mannitol did not significantly decrease FEV_1, but produced a mean of 8 coughs. At Visits 2 and 3, the subjects had spirometry measurements followed by inhalation of technetium-99 labelled sulfur colloid in isotonic saline. Images of the lung were taken every 20 seconds by a rotating gamma camera for 10 min to establish a baseline. The subjects received either mannitol by inhalation or an empty capsule and were asked to cough the same number of times as they had at Visit 1. After the intervention with mannitol or control plus coughing, the lung images at 20-second intervals were resumed for an additional 45 minutes. The total clearance of radioactivity at the end of 45 minutes was significantly higher after mannitol treatment than control plus coughing for both the asthmatic and normal subjects. For the asthmatic subjects, the mean total clearances were 55% and 34% for mannitol and control, respectively ($p < 0.002$), and for normal subjects, the values were 41% and 25% for mannitol and control, respectively ($p < 0.002$).

Since β_2-agonists and osmotic agents such as mannitol stimulate mucociliary clearance by different mechanisms that could potentially interact, Daviskas[15], studied the effects of inhaling terbutaline in combination with mannitol. Nine healthy and 11 mildly asthmatic subjects received treatments in which terbutaline or control was inhaled 10 minutes before mannitol, terbutaline was inhaled 5 minutes after mannitol, and terbutaline was inhaled 10 minutes after the control for mannitol (empty capsules plus coughing). The clearance of inhaled technetium-99 sulfur colloid was measured with a gamma camera. The mannitol-induced increase in mucociliary clearance was transiently inhibited by terbutaline pre-treatment, and transiently enhanced when terbutaline was administered after mannitol. Total clearance during 140 minutes produced by terbutaline plus mannitol was independent of the order of administration. It was concluded that although the timing of administration of terbutaline may transiently affect the rate of clearance produced by mannitol, the overall clearance was not changed.

Two double-blind placebo-controlled studies[25] investigating twice daily administration of 400 mg for two weeks in a total of 60 patients with bronchiectasis showed a significant improvement in quality of life, symptom score and sleep quality, with no serious adverse events, no change in sputum microbiology and no change in lung function.

Use of IDPM in Subjects with Cystic Fibrosis

To test whether mannitol may be useful in helping to clear the viscous bronchial mucus associated with cystic fibrosis; a pilot study was conducted with 12 adult subjects[16]. Similar to the study above, technetium-99 labelled sulfur colloid was administered and clearance of the radiolabel from the lung was measured with a gamma camera. Each subject received four treatments: 300 mg dry powder mannitol, empty capsules plus coughing, hypertonic saline (7 mL of 6% solution), and physiological saline (7 mL of 0.9%) plus coughing. The clearance of radioactivity from the lung was measured for 60 minutes after the end of administration of the

treatments. After the 60-minute interval, all subjects were requested to cough 100 times within the next 30 minutes, while the clearance continued to be measured. The total clearance at the end of 90 minutes was significantly higher for both mannitol and hypertonic saline compared to their respective control treatments. The mean clearance was 28% and 19% for the mannitol and empty capsule plus coughing, respectively ($p < 0.01$). The mean clearance was 31% and 21% for hypertonic saline and physiological saline plus coughing, respectively ($p < 0.01$). It was concluded that dry powder mannitol is a potential mucoactive agent in cystic fibrosis patients.

Phase II blinded, controlled, crossover study of 2 weeks treatment duration[17]

The study subjects that were randomised to treatments were well distributed with respect to age (8-48 years) and balanced with respect to gender. They were of small build and had a low body mass index (21/39 patients were less than the lower limit of normal). The FEV_1 at study entry was 64 ± 13% of predicted, with a minimum of 41% and a maximum of 91%, which classified the subjects as having mild to moderate disease. Approximately half the subjects were using concomitant RhDNase treatment. 49 subjects were enrolled in the study and 10 subjects were withdrawn before randomisation following a fall in FEV_1 of $\geq$15% from baseline during an Aridol challenge indicating bronchial hyperresponsiveness. 6 of these subjects had bronchial hyperresponsiveness despite having no history of active asthma and pre-medication with salbutamol. The mechanism for this response remains unclear, but rather than bronchoconstriction this might represent small airways collapse due to the frequency of FVC manoeuvres required before and during the Aridol challenge. Two children disliked the taste of IDPM and it made them too nauseous to continue. Two subjects had to stop the Aridol challenge because of severe cough, which had also been observed in previous studies. As a result of the severe cough in these 2 adults, the inhaler device used in adults was changed to a higher resistance device.

There were 7 serious adverse events recorded during the study with none being attributed as possibly or probably related to IDPM treatment. There were 3 withdrawals due to adverse events during the study after treatment randomisation. There were 2 withdrawals due to an exacerbation of respiratory infection while on treatment with IDPM, none while on treatment with control and one while in a washout phase. Sputum cultures did not show any deleterious effects of IDPM treatment, as no changes in sputum culture growth (either increases or decreases) were related to IDPM treatment. Equivalent numbers of patients changed from positive to negative growth and negative to positive growth in sputum cultures during both of the treatment periods. The vast majority of patients had no change in growth over the treatment period, and the majority of patients were positive for pathogens at entry to treatment. Vital signs, including SpO2, were also unchanged by treatment with IDPM. The safety profile for IDPM is considered to be suitable for more extended periods of treatment in subjects with cystic fibrosis.

Treatment with IDPM led to a significant increase in the FEV_1 on IDPM treatment (7 ± 1.9%, mean ± SE, $p<0.001$) and this increase was significant compared to the change on control treatment ($p<0.01$). The absolute increase in FEV_1 on IDPM treatment was 121 ± 33 mL (mean ± SE). There was no evidence of an effect of baseline FEV_1 on response to treatment. FEF_{25-75} also increased significantly while on IDPM treatment (15.5 ± 0.46 % (mean ± SE), $p<0.01$) and the increase was significant compared to that seen on control ($p<0.02$). FVC increased by 4.6%,

which was not a significant change, confirming that the increase in FEF_{25-75} was physiologically significant. The FEF_{25-75} reflects airflow in small airways and is probably an early abnormality in cystic fibrosis. Concomitant RhDNase treatment did not have a significant impact on the change in FEV_1 or FEF_{25-75} on IDPM treatment, suggesting there is an additive effect of the two treatments. Thus it is concluded that two weeks treatment with IDPM significantly improves measures of lung function related to small airways obstruction, and that this improvement is still apparent in the presence of concomitant RhDNase treatment. These changes are comparable to those reported for RhDNase treatment[18,19] and hypertonic saline treatment[19,20] and although the mechanism of effect may not be the same as RhDNase it is probably similar to hypertonic saline.

Treatment with IDPM also led to a significant difference in the change in respiratory symptom score compared with control. There was no difference observed in sinus symptom score. Respiratory symptom score probably reflects both lung function improvement as well as changes in sputum production and cough severity. While the difference in score change was significantly different on IDPM compared with control, it should be noted that the pre-post treatment change on IDPM did not in itself achieve statistical significance. There was no apparent improvement in sinusitis as assessed by the sinus symptoms score. Physical signs were assessed as part of the safety profile and were unchanged overall, except for chest auscultation which showed a significant improvement on IDPM over control. This physical sign improvement was concordant with the symptom changes.

Treatment with IDPM led to a significant improvement in the Cystic Fibrosis Questionnaire (CFQ-R) respiratory domain scores compared with control in the 14+ age group. Overall the respiratory domain scores were not significantly changed despite the trend. The reason for the difference between those younger and older than 14 is not known, but may relate to the questionnaire and its administration which are different according to the age group. No other domains changed on IDPM treatment to a significant extent. It is not unexpected that quality of life changes are not dramatic in this disease over such a short course of treatment.

It is concluded overall that IDPM was well tolerated with an acceptable safety profile and it provided a significant improvement in parameters of lung function related to small airways obstruction and a significant improvement in respiratory symptoms compared with control treatment. There was also a suggestion that health related quality of life might be improved. It is recommended that these findings support the assessment of IDPM in larger, longer term trials in CF patients with added measures of efficacy examined e.g. exacerbation rates.

1.3 Known and Potential Risks (and Benefits) to Human Subjects

Mannitol currently has a number of medical applications. It is used because it is inexpensive, has no known toxicity and has an excellent safety record. Mannitol is principally used to raise the osmolarity resulting in enhanced flow of water from tissues while remaining in the extracellular compartment. Mannitol is given orally in doses of up to 200g to induce diarrhoea for bowel preparation prior to diagnosis (colonoscopy) or surgery[21], and intravenously in a dose of 50 to 200g over a 12 hour period to induce diuresis or up to 0.25g/kg (i.e. approximately 16g for a 65kg subject) over 30 to 60 minutes to treat cerebral oedema[22].

In pharmaceutical preparations its primary use is as an excipient in tablets. Mannitol is also frequently used as an additive in the manufacture of foods such as baby milk formula[23] and confectionary. Mannitol has low energy value since it is largely eliminated from the body before any metabolism can take place. Mannitol is sweet tasting, and is used as a sweetening agent that is approximately as sweet as glucose and half as sweet as sucrose and imparts a cooling sensation in the mouth[24]. Another advantage to using mannitol in foodstuffs is that it is more slowly fermented by oral micro-organisms than glucose and this decreases the acidification and plaque formation on teeth. An intake of 20g is required to produce a laxative effect[24].

Because IDPM is a bronchoconstrictor in those with sub-optimally controlled asthma, it is important to detect and exclude all those who may be at risk of developing airway narrowing in response to inhaled mannitol. For these reasons, subjects will be administered a mannitol tolerance test using Aridol-MTT comprising of sequential inhalations of D-mannitol using a dry-powder inhaler. Aridol-MTT is an abbreviated version of the Aridol™ bronchial provocation test, that is, subjects receive 395mg rather than 635mg of D-mannitol. Procedural details are given in page 27 Section 3.3.8.5. Aridol™ is a registered bronchial provocation test in Australia, Sweden, Netherlands and Denmark.

IDPM may put subjects with hyperreactive airways at risk of airway narrowing. Typically these subjects have hypertrophied smooth muscle abundant with mast cells and eosinophils that react to the osmotic stimulus of mannitol by releasing mediators that cause the muscle to contract and narrow the airways. This is a typical response in asthmatic subjects with sub-optimal control. Subjects with asthma who are well controlled with inhaled cortico-steroids, do not develop bronchoconstriction in response to mannitol, moreover, healthy control subjects are similarly non responders[13].

Cough tends to occur when inhaling mannitol and in some cases has been severe enough to be reported as an adverse event. Some subjects given compassionate use access to IDPM in Australia have reported an apparent tolerance to IDPM as reflected by a significant reduction in cough when using the product over a period of 2 weeks and longer.

Nausea and vomiting and a sore, dry throat have been reported in small numbers of patients in short term studies. It is recommended that subjects have a drink of water to rinse mannitol from the oral cavity and oesophagus after inhalation.

Mannitol by its osmotic nature increases the water content in nasal secretions when exhaled through the nose. When administered as a bronchial challenge, some subjects experience a 'runny nose' while subjects receiving therapeutic doses for mucociliary clearance report a 'clearing of thick sticky nasal mucous' allowing them to breathe more easily through the nose.

The benefits of clearing bronchial secretions would be expected to include improvements in lung function, reduction in cough and inflammation with the potential for improvement in quality of life and reduced incidence of infections. Dry powder mannitol has been shown to improve mucus clearance in patients with bronchiectasis and CF within 90 minutes after a single administration[14,16], and improve FEV_1 when used over a 2 week period[17]. It is therefore potentially an agent which could improve mucus clearance in diseases such as bronchiectasis,

cystic fibrosis, sinusitis and chronic bronchitis and provide associated benefits in the longer term. Moreover, it is highly portable and convenient, and possesses none of the infection control issues or requirement for electricity associated with wet aerosols. It is this potential and the paucity of known adverse effects that support a longer term investigation of its use in cystic fibrosis patients.

1.4 Selection of Drugs and Doses

IDPM will be administered as a dry powder for oral inhalation at 400 mg or matched control (sub therapeutic dose), twice a day for 26 weeks. Previously, in acute mucociliary clearance studies[14, 26, 27], 320 - 400 mg has been demonstrated as being efficacious and safe, and in a two week study was also shown to be efficacious and safe[17]. An open label two week dosing study (ongoing) showed a significant increase in FEV_1 at 400 mg BD compared with a sub-therapeutic dose given BD, whereas there was no significant difference between 240 mg BD and control. In addition 2 x 26 week open label phases will provide data on the long term safety and tolerability of IDPM.

1.5 Compliance Statement

The investigator(s) is responsible for performing the study in accordance with this protocol and the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP), and for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this study in accordance with the protocol will be documented in study agreements with the sponsor, and other forms as required by national authorities in the country where the study centre is located.

The investigator(s) is responsible for ensuring the privacy, health, and welfare of the subjects during and after the study, and must ensure that fully functional resuscitation equipment and personnel trained in its proper use are immediately available in case of a medical emergency. The investigator(s) must be familiar with the background and requirements of the study and with the properties of the study drug as described in the Investigator's Brochure.

The principal investigator at each centre has the overall responsibility for the conduct and administration of the study at that centre, and for contacts with study centre management, the Independent Ethics Committee (IEC), and with local authorities.

1.6 Population Studied

Cystic fibrosis, aged $\geq$6 years, baseline FEV_1 $\geq$30% - 90% predicted, not be pregnant or breast feeding, no intolerance to mannitol or beta agonists, no concurrent use of hypertonic saline or beta blockers for the study duration.

Patients will be recruited that are either taking concurrent RhDNase or not using it at all. The number of concurrent RhDNase using subjects recruited will be sufficient to power the study to detect changes in this subgroup as well as the total population.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Study Objectives

2.1.1 Primary Objective:

- To determine the effect of IDPM compared to control on FEV_1 in patients with CF

2.1.2 Secondary Objectives:

- To determine the effect of IDPM compared to control on FEV_1 in patients with CF on existing RhDNase treatment. (key objective)

To assess whether IDPM treatment:

- Reduces pulmonary exacerbations in those taking RhDNase as a sub-group and in the total cohort (key objective)
- Improves quality of life (key objective)
- Reduces days on IV antibiotics, rescue oral or inhaled antibiotics
- Reduces days in hospital due to pulmonary exacerbations
- Improves other measures of lung function
- Demonstrates an appropriate safety profile (adverse events, haematology, biochemistry, change in bronchodilator response, sputum microbiology, physical examination)
- Reduces hospital and community care costs

2.2 Purpose of Study and Rationale

The purpose of this study is to determine the efficacy and safety of chronic treatment with IDPM compared with control, in subjects with cystic fibrosis. Previous studies have demonstrated an improvement in lung function related to small airways obstruction and a significant improvement in respiratory symptoms compared with control treatment and improvement in quality of life after a 2 week treatment with IDPM. This current study seeks to support these early findings and to extend the evidence to support its use as a mucoactive therapy in cystic fibrosis. In particular, the hypothesis that enhanced mucus clearance will improve the lung function and clinical presentation in this population, will be investigated. We also hypothesize that enhanced mucociliary clearance will result in a sustained reduction in mucus load, thus providing less opportunity for bacteria to proliferate, affording a reduction in antibiotic use and hospitalisations. In summary, we aim to demonstrate that IDPM facilitates an improvement in lung function (FEV_1), a reduction in pulmonary exacerbations and an improvement in quality of life. This study also aims to demonstrate that medium and long term IDPM treatment is well tolerated physiologically.

3 STUDY DESIGN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint**:**

- Change in absolute FEV_1

3.1.2 Secondary Endpoints:

Measures of Efficacy

- Change in absolute FEV_1(RhDNase group)
- Pulmonary exacerbations in those taking RhDNase as a sub-group and in the total cohort
- Quality of Life Scores using Cystic Fibrosis Questionnaire-R
- Rescue antibiotic use (number of agents course and days of use)
- Change in FVC, FEF_{25-75} from baseline
- Days in hospital due to pulmonary exacerbations
- Cost effectiveness including total costs of hospital and community care

Measures of Safety

- Adverse events
- Laboratory safety tests: full blood count, urea and electrolytes, liver function tests
- Qualitative sputum microbiology
- Bronchodilator response before and after treatment (to exclude treatment acquired inflammation)
- Physical examination

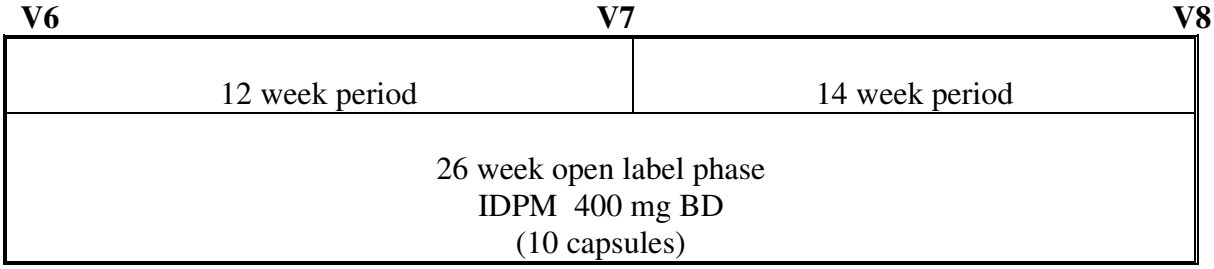
3.2 General Design and Study Schema

This is a double blind, randomised, parallel arm, controlled, intervention clinical trial. At screening, eligible subjects will be 3:2 randomised to receive 26 weeks of IDPM 400mg BD or matched control. Following successful completion of the initial 26 week phase, a 2 visit, 26 week, open label phase will be offered to qualifying subjects (Diagram 1). On completion of this 26 week open label phase an extra 26 week open label phase with two visits will be offered to qualifying subjects (Diagram 2). In the open label phases, all subjects will receive active treatment at 400mg twice a day.

Diagram 1. Study Schema

V0	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**
Day 0 2 wk period	6 week period	8 week period	12 week period	12 week period	14 week period	
Screening	26 week blinded phase			26 week open label phase		
	IDPM 400 mg BD (10 capsules)			IDPM 400 mg BD (10 capsules)		
	Control BD (10 capsules)					

Diagram 2. Study Schema: Second Open Label Phase



Summary of Visit Procedures

This study consists of 5 study visits over 28 weeks for the base safety and efficacy study and an additional two visits in each of two 26 week open label phases (initial open label phase and an extension open label phase) (see Appendix 1: Time and Events Schedule). The procedures to be undertaken at each visit are as follows:

3.2.1 Visit 0 - Screening

Each potential subject will be examined to determine eligibility for the study. The following activities will be performed at this visit:

- Obtain written informed consent - this must be obtained before any study-related procedures, including medication withholding requests, are undertaken. This may be done prior to V0.
- Review inclusion / exclusion criteria, including but not limited to:
  - pulmonary function tests
  - urine pregnancy test (for women of child-bearing potential).
  - physical examination / vital signs
- Collect sputum sample (prior to Aridol-MMT)
- Obtain demographic information:
  - date of birth
  - height and weight
  - race
  - gender
  - age at diagnosis
- Review and record concomitant medications for the previous 3 months
- Review medical history
- Test for airway hyperresponsiveness (with Aridol-MTT)
- Randomise eligible subjects
- Collect venous blood sample for renal function tests, full blood count, liver function tests.

NB: Screening bloods may be omitted if they have been performed in the previous 3 months and the results are available. There is no need to collect blood for ineligible subjects.

3.2.2 Visit 1

Visit 1 should occur 2 weeks post screening visit (+21days)
The following procedures will be performed:

- Subject/parent to complete age appropriate Cystic Fibrosis Questionnaire
- Review concomitant medications and adverse events
- Conduct physical examination including: chest sounds, weight, BP, HR, O_2 sat, temp, respiratory rate
- Medication withholding periods before spirometry must be complied with or subject should be postponed
- Perform pulmonary function testing (FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75})
- Perform forced oscillation technique (FOT) (participating sites only)
- Collect sputum sample for microbiology (culture and sensitivity)
- Conduct bronchodilator response test. The medications listed in Table 1 must be withheld prior to the test. Subjects who fail to withhold medications as directed must be rescheduled.
- Administer initial dose of study medication (IDPM / control) according to 'Study Drug Administration Procedure' (see 3.3.20) and randomisation group. This should **follow** the bronchodilator response test to ensure that subjects have been premedicated with bronchodilator.
- Collect all sputum produced during and for 30 mins post study medication, then weigh collection.
- Perform post dose FEV_1
- Dispense study medication according to randomisation schedule
- Dispense bronchodilator. Bronchodilator is to be used approximately 5 -15 mins prior to each dose of study medication. The default bronchodilator for this study is 4 x 100 µg salbutamol.
- Issue study diary

3.2.3 Visit 2

Visit 2 should occur on completion of 6 weeks study treatment (-7 to +14 days)
The following procedures will be performed:

- Medication withholding periods before spirometry must be complied with or subject should be postponed
- Review concomitant medications and adverse events
- Conduct physical examination including: chest sounds, weight, BP, HR, O_2 sat, temp, respiratory rate
- Perform pulmonary function testing (FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75})
- Perform FOT (participating sites only)
- Pulmonary exacerbations review (refer to study diary)
- Medical resource use review (refer to study diary)
- Dispense study medications and bronchodilator
- Collect sputum sample for microbiology (culture and sensitivity)
- Conduct drug accountability

3.2.4 Visit 3

Visit 3 should occur at the end of 14 weeks study treatment (±14 days)
The following procedures will be performed:

- Medication withholding periods before spirometry must be complied with or subject should be postponed
- Administer age appropriate Cystic Fibrosis Questionnaire
- Review concomitant medications and adverse events
- Conduct physical examination including: chest sounds, weight, BP, HR, O_2 sat, temp, respiratory rate
- Perform pulmonary function testing (FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75})
- Perform FOT (participating sites only)
- Following pre-medication with bronchodilator, administer subject's usual dose of IDPM/control in clinic
- Collect all sputum produced during and for 30 mins post study medication. Weigh collection.
- Perform post dose FEV_1
- Collect sputum sample for microbiology (culture and sensitivity)
- Pulmonary exacerbations review
- Medical resource use review
- Dispense study medications and bronchodilator
- Conduct drug accountability

3.2.5 Visit 4

Visit 4 should occur at the end of 26 weeks of study treatment (±14 days)
The following procedures will be performed:

- Medication withholding periods before spirometry must be complied with or subject should be postponed
- Administer age appropriate Cystic Fibrosis Questionnaire
- Review concomitant medications and adverse events
- Conduct physical examination including: chest sounds, height, weight, BP, HR, O_2 sat, temp, respiratory rate
- Perform pulmonary function testing (FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75})
- Perform FOT (participating sites only)
- Conduct bronchodilator response test. The medications listed in Table 1 must be withheld prior to the test.
- Pulmonary exacerbations review
- Medical resource use review
- Collect blood sample for renal and liver function, full blood count
- Collect sputum sample for microbiology (culture and sensitivity)
- Conduct drug accountability

For those that wish to continue in the 1st 26 week open label period

- Consent subject for the 1st 26 week open label period (if not already performed)
- Conduct urine pregnancy test (females at risk only)
- Administer initial dose of open label IDPM. This should **follow** the bronchodilator

response test to ensure that subjects have been premedicated with bronchodilator.
- Perform post dose FEV_1
- Dispense study medications and bronchodilator
- Issue 2nd study diary if required (collect 1st diary if full)

Phone Call
Four weeks into the open label phase of the study, the investigator or designate, will call the participant to enquire as to their health with particular regard to response to the open label medication. If problems are noted and an unscheduled visit is deemed necessary, this should be arranged.

For those not wishing to continue in open label arm
- Collect study diary
- Discharge subject from study

Open Label Visits (1st 26 week period)

3.2.6 Visit 5

Visit 5 should occur at the end of 38 weeks of study treatment. (12 weeks post visit 4) (±14 days)
The following procedures will be performed:
- Medication withholding periods before spirometry must be complied with or subject should be postponed
- Review concomitant medications and adverse events
- Conduct physical examination including: chest sounds, weight, BP, HR, O_2 sat, temp, respiratory rate
- Perform pulmonary function testing (FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75})
- Pulmonary exacerbations review
- Medical resource use review
- Dispense study medications and bronchodilator
- Collect sputum sample for qualitative microbiology
- Conduct drug accountability

3.2.7 Visit 6

Visit 6 should occur at the end of 52 weeks of study treatment (14 weeks post visit 5) (±14 days)
The following procedures will be performed:
- Medication withholding periods before spirometry must be complied with or subject should be postponed
- Review concomitant medications and adverse events
- Conduct physical examination including: chest sounds, height, weight, BP, HR, O_2 sat, temp, respiratory rate
- Perform pulmonary function testing (FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75})
- Pulmonary exacerbations review

- Medical resource use review
- Collect sputum sample for qualitative microbiology
- Collect blood sample for renal and liver function, full blood count
- Conduct drug accountability
- Collect diary

For those that wish to continue in the 2nd 26 week open label period

- Consent subject for the 2nd 26 week open label period (if not already performed)
- Conduct urine pregnancy test (females at risk only)
- Issue another study diary
- Dispense study medications and bronchodilator

For those not wishing to continue in 2nd 26 week open label period

- Discharge subject from study

Open Label Visits (2nd 26 week period)

3.2.8 Visit 7

Visit 7 should occur at the end of 64 weeks of study treatment. (12 weeks post visit 6) (±14 days)
The following procedures will be performed:

- Medication withholding periods before spirometry must be complied with or subject should be postponed
- Review concomitant medications and adverse events
- Conduct physical examination including: chest sounds, weight, BP, HR, O_2 sat, temp, respiratory rate
- Perform pulmonary function testing (FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75})
- Pulmonary exacerbations review
- Medical resource use review
- Dispense study medications and bronchodilator
- Collect sputum sample for qualitative microbiology
- Conduct drug accountability

3.2.9 Visit 8

Visit 8 should occur at the end of 78 weeks of study treatment (14 weeks post visit 7) (±14 days)
The following procedures will be performed:

- Medication withholding periods before spirometry must be complied with or subject should be postponed
- Review concomitant medications and adverse events
- Conduct physical examination including: chest sounds, height, weight, BP, HR, O_2 sat, temp, respiratory rate
- Perform pulmonary function testing (FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75})
- Pulmonary exacerbations review

- Medical resource use review
- Collect sputum sample for qualitative microbiology
- Collect blood sample for renal and liver function, full blood count
- Conduct drug accountability
- Collect diary
- Discharge subject from study

3.2.10 Early Withdrawal Assessments

Any subject withdrawing early from the study should be asked to contribute a blood sample (haematology and biochemistry) for safety follow-up, providing they have received at least 2 months of study medication. Where a visit is due, study procedures should be completed as far as practical. If withdrawal occurs between visits, the next study visit procedures should be conducted where practical. Drug collection, compliance and accountability should occur.

3.3 Study Procedures

3.3.1 Informed Consent

Informed consent must be undertaken prior to conducting any study related procedures including the withholding of medications. Consent for the 1st open label phase may be sought at any time prior and up to visit 4. Consent for the 2nd open label period should be obtained at visit 6. As with any research study, subjects are free to withdraw consent at any time without prejudice. A single consent form may incorporate both study components if desired (blinded and 1st open label phase), GCP Guidelines recommend that informed consent should be obtained so that ample time and opportunity is given for subjects to enquire about details of the trial and to decide whether or not to participate. Refer to 2005 Code of Federal Regulations & ICH Guidelines: ICH GCP 4.8.

3.3.2 Eligibility Criteria

Applies to V0

Subjects will be reviewed for eligibility against the study inclusion and exclusion criteria.

3.3.3 Medical History

Applies to V0

A comprehensive medical history will be undertaken by the investigator to determine past and current medical conditions and procedures.

3.3.4 Demographic Information

Applies to V0

The following information will be collected: date of birth, height and weight, race, gender, age at diagnosis.

3.3.5 Concomitant medications

Applies to V0 with updates every visit thereafter.
Medication use, current, and in the preceding 3 months will be noted. Generic names are to be used, and start and stop dates, total daily dose, route and indication should be recorded. "Alternative therapies" are not to be recorded in the CRF.

NB. Where possible the use of all concomitant medications at the start of the treatment period should be maintained throughout the treatment period, and wherever possible, institution of new concomitant medications should be avoided.

3.3.6 Physical Examination and Vital Signs

Applies to all visits
A physical examination as follows:
Vital signs (BP, HR, RR, $Sp0_2$, temperature), chest auscultation and weight. Height will be recorded at screening, V4, V6 and V8. The physical examination should be conducted by a physician, but where timing prohibits this, a suitably trained nurse or respiratory therapist may undertake this task. If any doubt exists about the physical status of the subject (including determining exacerbations and respiratory tract infections), the physician should be consulted.

3.3.7 Spirometry

Applies to all visits

3.3.7.1 Patient Considerations

Where possible, pulmonary function testing should be performed as close as possible to the same time of the day at each visit. All visits should coincide with the trough treatment effect i.e. at least 12 hours since the previous medication dose. The order and timing of all concurrent treatments e.g. postural drainage and medications, and required withholding of concurrent medications should be the same for every visit.

All pulmonary function testing should be done in the sitting position.

Subjects should avoid the activities listed before lung function testing;

- smoking within 1 hour of testing
- consuming alcohol within 4 hours of testing
- performing vigorous exercise within 30 min of testing

Medications listed in Table 1 must be withheld prior to all spirometry (Visit 1 onwards).
Subjects who fail to withhold medications as directed must be rescheduled.

Table 1: Medications That May Influence Spirometry Results

Medication	Minimum time interval from last dose until spirometry
IDPM or control (study medication)	12 hours
Short acting β_2 agonists eg salbutamol (Ventolin, Respolin, Airomir, Asmol, Epaq, Resmax, Combivent, Apsomol, Asthmalitan, Broncho Fertiginhalat / Inhalat, Bronchospray, Cyclocaps, Loftan, Pädiamol, Pentamol, Salbu-Fatol, Salbu Novolizer, Salbubronch,. Salbuhexal, Salbulair, Salbulind, Salbupp, Salbusandoz, Salbutamol AL / Atid / Azu / ct / ratiopharm / Sandoz / Stada / Trom, Sultanol, Ventilastin, Volmac); terbutaline (Aerodur, Arubendol, Asthmoprotect, Bricanyl, Contimit, Terbul, Terbutalin AL / ct / ratiopharm / Stada / Terbuturmant	6 hours
Long acting β_2 agonists *eg salmeterol (Aeromax, Serevent); eformoterol (Oxis, Foradil)*	12 hours
Combination drugs *e.g. Fluticasone and salmeterol (Seretide, Advair, Atmadisc, Viani), budesonide and eformoterol (Symbicort)*	12 hours

3.3.7.2 Limitations of Methodology/Validation of Results

Spirometry is an effort-dependent test that requires very careful instruction and cooperation of the test subject. Inability to perform acceptable manoeuvres may be due to poor subject motivation or failure to understand instructions. Physical impairment and young aged children (e.g. children <6 years of age) may also limit the subject's ability to perform spirometric manoeuvres. These limitations do not preclude attempting spirometry, but should be noted and taken into consideration when the results are interpreted.

The results of spirometry testing should meet the following criteria for number of trials, acceptability, and repeatability. The acceptability criteria should be applied before repeatability is checked.

Number of trials: A minimum of 3 acceptable FVC manoeuvres should be performed. If a subject is unable to perform a single acceptable manoeuvre after 8 attempts, testing should be discontinued. However, after additional instruction and demonstration, in some cases more manoeuvres may be performed depending on the subject's clinical condition and tolerance.

Acceptability: A good 'start-of-test' includes:

- An extrapolated volume of ≤5% of the FVC or 150 ml, whichever is greater
- No hesitation or false start
- A rapid start to rise time (e.g. a short peak expiratory flow time)

Acceptability: No cough, especially during the first second of the manoeuvre.
Acceptability: No early termination of exhalation:

- A minimum exhalation time of 6 seconds (3 seconds for children) is recommended, unless there is an obvious plateau of reasonable duration (e.g. no volume change for at least 1 second) or the subject cannot or should not continue to exhale further
- No manoeuvre should be eliminated solely because of early termination. The FEV_1 from such manoeuvres may be valid, and the volume expired may be an estimate of the true FVC, although the FEV_1/FVC and FEF_{25-75} may be overestimated

Repeatability: Two highest FVCs within 0.150 L, Two highest FEV_1s within 0.150 L. Or if FVC < 1.0 L, then FVC and FEV_1 repeatability to be better than 0.100 L.

Quality Control
To facilitate quality spirometry, the following will be implemented:

- Regular review of spirometric measures will be performed and feedback will be provided to sites.
- Standardised spirometers that meet ATS/ERS requirements will be used.
- All lung function measures as they apply to this study will be performed on a dedicated spirometer. Each subject is to be assessed using the study spirometer only.
- Predicted tables will be standardised across sites.
- Personnel performing spirometry must be trained and qualified to do so.

3.3.7.3 Reporting of Spirometry Results

The largest FVC and FEV_1 (at body temperature, ambient pressure, saturated with water vapour, (BTPS)) should be reported even if they do not come from the same curve.

Other reported measures (e.g. FEF_{25-75} and instantaneous expiratory flow rates, such as FEF_{max} and FEF_{50}) should be obtained from the single acceptable 'best-test' curve (e.g. largest sum of FVC and FEV_1) and reported at BTPS.

All values should be recorded and stored so that comparison for reproducibility and the ability to detect spirometry induced bronchospasm (as evidenced by a worsening in spirometric values with successive attempts and not related to fatigue) are simplified.

The time of day, equipment or instrumentation used, beginning and end times of tests and name of the technician administering the test should be recorded.

Flow volume curves should be printed for data verification.

3.3.7.4 Selecting Spirometry for Data Entry into the CRF

The following spirometry results demonstrate how site staff will select the correct data:

Time	Effort	FEV_1	FVC	FEV_1/FVC%	FEF_{25-75}	PEF
10.48	1	2.45	3.70	66	1.75	6.7
10:50	2	2.33	3.69	63	1.70	6.0
10.52	3	2.41	3.76	64	1.79	6.5

The results that must be used in analysis are:

- **FEV_1**: 2.45 (best individual result)
- **FVC**: 3.76 (best individual result)
- **PEF**: 6.7 (best individual result)
- **FEV_1/FVC%**: 2.45 / 3.76 = 65 (best individual FEV_1 / best individual FVC (may be from separate efforts)
- **FEF_{25-75}**: 1.79 (from the effort with the highest FVC+FEV_1) - see below for example:
  Effort 1: 2.45 + 3.70 = 6.15
  Effort 2: 2.33 + 3.69 = 6.02
  Effort 3: 2.41 + 3.76 = 6.17 (record value of 1.79)

All of the above are from acceptable efforts. The best single effort will be determined based on the highest combined value for FEV_1 and FVC.

3.3.7.5 Adult and Child Predicted Tables

Screening predicted values will be based on the predicted tables currently recommended by the United States CF Foundation[28,29]. Adjustments for race should be used when determining normal predictive values.

3.3.8 Aridol-MTT Procedure for Airway Hyperresponsiveness

Applies to visit 0

The Aridol-MTT procedure identifies subjects who have airway hyperresponsiveness in response to inhaled mannitol. Airway hyperresponsiveness is determined by measuring the degree of bronchoconstriction that occurs following sequential administrations of D-mannitol.

3.3.8.1 Safety Guidelines and Equipment Requirements

As is standard in administering agents that have the potential to cause bronchoconstriction, a physician, appropriately trained to treat acute bronchospasm, including the use of resuscitation equipment, must be available to respond to an emergency.

As a minimum, the person conducting the Aridol-MTT procedure must:

- Be proficient at performing spirometry
- Be familiar with safety and emergency procedures
- Know when to stop further testing
- Be proficient in the administration of inhaled bronchodilators and other rescue medications and equipment
- Where possible the person conducting the Aridol-MTT and the study co-ordinator should not be the same person. It is preferable to have these roles carried out by separate individuals.

The following equipment should be available during the Aridol-MTT procedure:

- Aridol-MTT kit with Osmohaler-HR
- Bronchodilator metered-dose inhalers and spacers
- A spirometry system that meets ERS/ATS requirements. The spirometer will be provided to sites for study use.
- Calculator and 60 second timer
- Pulse oximeter
- Epinephrine, atropine and oxygen

3.3.8.2 Monitoring Subject Safety during Aridol-MTT Procedure

Subjects should be monitored during the Aridol-MTT procedure by following the safety schedule listed in table 2.

Table 2: Monitoring Subject Safety during Aridol-MTT Procedure

Parameter	Baseline (pre-bronchodilator)	At each dose step	At midway point and end of test	15 min post test *
SpO_2	X	X		X
FVC	X			X
FEV_1	X		X	X
Clinical signs &symptoms		X		X

*** Post test FVC should be measured for all patients including those with +ve tests, -ve tests and incomplete tests**

3.3.8.3 Aridol-MTT Technical Considerations

- The gelatin capsules may fragment if pierced more than once.
- To facilitate the development of an osmotic gradient within the airway, there should be minimal delay between subsequent doses.
- Static charge can be problematic with dry powders, particularly in low humidity environments. If the capsule fails to spin in the device on inhalation tilt the device nozzle down and tap the base to drop the capsule into the spinning chamber.
- Warn your subject to expect cough. Cough can be controlled by slowing the rate of inhalation, while still ensuring that the flow rate is enough to facilitate emptying the capsule. Cough tends to lessen with subsequent administrations.
- The sweet taste may be offset by offering a drink of water during the procedure. Water can also be given following the procedure to clear residual powder from the oropharynx.
- Exhalation through the nose may lead to a small degree of rhinorrhea.
- Subject should never exhale into the device.

3.3.8.4 When to Stop the Aridol-MTT Procedure

Stop the Aridol-MTT procedure if:

- The subject's oxygen saturation falls below 89% (Record as an adverse event)
- Cough is highly distressing or vomiting occurs (Record as an adverse event)
- Subject's FEV_1 has fallen $\geq$20% (from baseline) at step 5 of the procedure
- A total of 395mg Aridol-MTT has been administered

3.3.8.5 Aridol-MTT Procedure

1. Perform baseline spirometry and measure SpO_2. Multiply the patient's best FEV_1 by 0.80 and 0.50 to obtain the 20% and 50% fall in FEV_1 values respectively.
2. Premedicate patient with 4 x 100 µg salbutamol and wait 5–15 min
3. Administer a total of 35 mg (5 + 10 + 20mg) Aridol-MTT as follows:
   i. inhale contents of 5mg capsule in a controlled, deep inhalation, breath hold for 5 seconds, then exhale
   ii. immediately inhale contents of 10 mg capsule, 5s breath hold, exhale
   iii. immediately inhale contents of 20 mg capsule, 5s breath hold, exhale
   iv. Wait 60 seconds, then monitor oxygen saturation

   If SpO_2 <89%, discontinue test and treat as required. Otherwise:

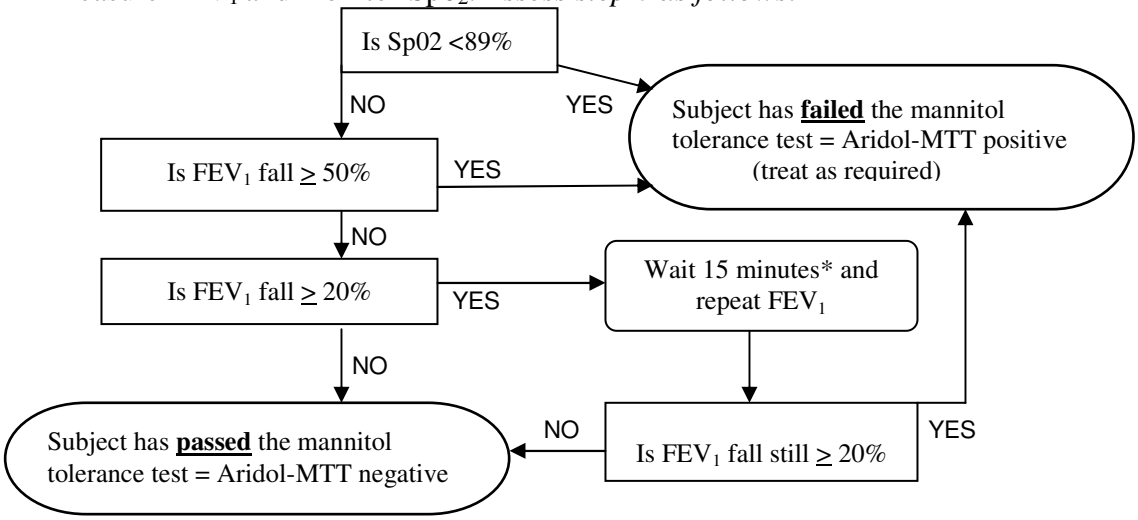
4. Administer an additional 80mg Aridol-MTT (2 x 40mg) as above. Wait 60 seconds, monitor oxygen saturation.

   If SpO_2 <89%, discontinue test and treat as required. Otherwise:

5. Administer an additional 120mg Aridol-MTT (3 x 40mg) as above. Wait 60 seconds, measure FEV_1 and monitor oxygen saturation (this is the test's midway point).

   If FEV_1 fall is ≥20% (from baseline) or SpO_2 <89%, discontinue test and treat as required. Otherwise:

6. Administer an additional 160mg Aridol-MTT (4 x 40mg) as above. Wait 60 seconds, measure FEV_1 and monitor $Sp0_2$. *Assess step 6 as follows:*



7. Measure FEV_1 15 mins post test completion (all patients irrespective of result or completion point)

* consider using PEP mask /Acapella/ cough clearance to facilitate airway opening.

Aridol-MTT Assessment

The Aridol-MTT procedure should be assessed as follows:

Aridol-MTT Positive Test

1. The subject's oxygen saturation falls below 89% (record as adverse event)
2. Subject's FEV_1 has fallen $\geq$20% (from baseline) at midpoint (step 5)
3. Subject's FEV_1 has fallen $\geq$20% (from baseline) at end of test (step 6) and **does not** return to <20% within 15 minutes
4. Subject's FEV_1 has fallen $\geq$50% (from baseline) at end of test (step 6)

Aridol-MTT Negative Test

1. A total of 395mg Aridol-MTT has been administered (and no positive criteria have been met)
2. Subject's FEV_1 has fallen $\geq$20% (from baseline) at end of test (step 6) and **has** returned to <20% within 15 minutes

Aridol-MTT Incomplete Test

1. Cough is highly distressing or vomiting occurs during the procedure (record as adverse event)

Caution

If the subject shows clinical signs and symptoms of hypoxemia or bronchoconstriction eg wheeze, dyspnoea, accessory muscle use, sternal retraction or shortness of breath, measure FEV_1 and treat accordingly.

3.3.9 Bronchodilator Response Test

Applies to visits 1 and 4

To demonstrate that IDPM does not sensitise the airways with chronic use, subjects are to have the bronchodilator response measured at visit 1, prior to receiving the initial dose of study medication. This test will be repeated at visit 4. For those routinely taking bronchodilators, withholding periods as indicated in Table 1 will apply before procedure.

Subjects, who have taken any of the medications listed in Table 1 within the withholding periods, are asked to return for the bronchodilator response test after the withholding time has expired. **The test is invalid if compliance with these withholding periods is not 100%.**

Procedure

1. Obtain **baseline spirometry** (FVC) and oxygen saturation. The baseline FEV_1 is obtained from the FVC.
2. Administer 4 x 100 µg salbutamol MDI via spacer. Alternative bronchodilators may be used if patient preferred. Wait 15 minutes then perform post bronchodilator FEV_1.

3.3.10 Pregnancy Testing

Applies to visits 0, 4 and 6

A urine pregnancy test will be conducted at screening and at V4 where the subject chooses to continue in the 1st open label phase and at V6 if continuing in the 2nd open label phase. Applies to women of reproductive age at risk of pregnancy (in the investigator's opinion) only.

3.3.11 Contraception during the Study

Females at risk of pregnancy should use an effective form of contraception to prevent pregnancy e.g. oral contraceptive, condom, IUD, injectable contraceptive, diaphragm. Male subjects have no contraceptive restrictions as they pertain to this study medication.

3.3.12 Cystic Fibrosis Questionnaire - Revised

Applies to visits 1, 3 and 4

The Cystic Fibrosis Questionnaire is a disease specific, developmentally appropriate questionnaire designed to measure the physical, emotional and social impact of CF on patients and their families. It should be administered in a quiet room prior to other study related procedures where possible. The following formats apply:

US/English Version(s)[30]:

- Ages 6 – 11: Administered by an interviewer
- Ages 12-13: Self report format
- Ages 14 and over: Self report format
- Parent version: For parents of children aged 6 – 13 years

If a child has a birthday anytime between visit 1 and visit 4 that promotes them into an older age category eg a 13 year old turns 14, that child should continue to complete the original format questionnaire eg. 12 -13 years format (US/English). The parent of that child should continue to complete the Parent version.

3.3.13 Blood Samples

Applies to visits 0, 4 , 6 and 8.

Subjects will be asked to provide a blood sample to be analysed at the institutional laboratory for the factors listed in Table 3. Sites will provide a list of reference ranges from the laboratory conducting these tests. The V0 blood sample should only be collected from Aridol-MTT negative subjects.

If the required blood tests have been performed in the 3 months prior to visit 0, and providing the results are available for entry into the study record, repeated blood tests are not required. To minimize the discomfort associated with needle sticks in children, a topical anaesthetic may be applied at an appropriate time prior to blood draws.

3.3.14 Abnormal Blood Results

Results outside reference ranges post screening, will be listed as adverse events providing they were not present at visit 0 and they are determined to be clinically significant by the investigator. Abnormal results detected at visit 0 will be listed as a pre-existing medical

condition.

Table 3: Haematology, Renal and Liver Function Tests

Full Blood Count	Liver Function Tests	Urea and Electrolytes
Haemoglobin (Hb)	Albumin	Sodium
Red Cell Count	Globulin	Potassium
Hematocrit	Total protein	Chloride
Mean Corpuscular Volume	Bilirubin total	Bicarbonate
Mean Corpuscular Haemoglobin	Gamma GT	Urea
Mean Corpuscular Haemoglobin Concentration	Alkaline Phosphatase	Creatinine
Red cell Distribution Width	Lactate Dehydrogenase	Calcium
White Cell Count	Alanine Transaminase	Phosphate
Neutrophils	Aspartate Amino Transferase	Uric acid
Lymphocytes		Magnesium
Monocytes		
Eosinophils		
Basophils		
Platelet count		

3.3.15 Sputum Collection for Qualitative Microbiology

Applies to all visits

Note: The Visit 0 microbiology sputum sample should be taken **before** administration of the Aridol-MTT procedure and will represent the baseline sample. **Nebulised hypertonic or normal saline should NOT be used to induce sputum.**

Sputum samples may be collected at home prior to the study visit if providing sputum on demand is problematic. Samples collected at home should not be greater than 24 hours old and must be refrigerated at all times. Sterile sample containers should be given to subjects for at home collections. For samples collected at home, the following applies:

- collect samples as close as possible to the next clinic visit and refrigerate
- collect in sterile sample containers and label with collection date, time and name
- transport sample in an insulated container with ice brick to clinic

If sputum samples CANNOT be collected as above, a pharyngeal throat swab should be substituted.

Microbiology Collection Procedure

1. Provide the subject with a cup of water and an empty cup. Ask the subject to rinse and gargle and spit in empty cup (to be done 3 times). This will eliminate squamous cell contamination of the specimen.
2. Dispose of cup. Subject may retain a cup of water to drink during the procedure.
3. Instruct and demonstrate how to obtain sputum from the lungs by coughing and clearing the throat (deep cough and hack!).

4. Ask subjects to cough, clear their throat and deposit all or any oral contents into the specimen container. Listen to the subject to ensure the sample is from the lungs and not post nasal secretions.
5. Once an adequate specimen has been obtained, label the specimen jar as per protocol (including subject name, date of birth, date and time), place in specimen bag and refrigerate.
6. Contact lab staff for immediate pick up of specimen.
7. Lab to plate for microbiology, culture and sensitivity according to local laboratory standard operating procedures.

3.3.16 Antibiotic Use

The use of rescue antibiotics is an outcome measure and as such must be carefully monitored and documented. This will include all nebulised antibiotics, oral and intravenous use. Subjects will be asked to keep a diary record of all antibiotic use while in the study. This will include the antibiotic name, indication for use, the dose and the start and stop dates. Study co-ordinators will track all antibiotic use, noting the diary records as well as outpatient clinic and hospital records. Routine antibiotic use will be distinguished from rescue antibiotics.

3.3.17 Pulmonary Exacerbations

A protocol defined pulmonary exacerbation occurs when subjects are treated with intravenous antibiotics for **four or more** of the following twelve signs or symptoms [7]:

1. change in sputum production (volume, colour, consistency)
2. dyspnoea
3. new or increased haemoptysis
4. malaise, fatigue or lethargy
5. fever ($\geq 38^{o}C$)
6. anorexia or weight loss
7. sinus pain or tenderness
8. change in sinus discharge
9. FVC or FEV_1 decreased by $\geq$10% from previous recorded value
10. radiographic signs indicative of pulmonary infection
11. increased cough
12. changes in physical examination of the chest

Pulmonary exacerbations are expected to occur as part of the disease but will be recorded as adverse events. Expedited reporting of serious exacerbations to Regulators and Ethics Committees will only be carried out if the exacerbation is clinically different to that normally expected in a particular subject (e.g. more severe). In such cases, the difference should be noted on the AE form.

3.3.18 Hospitalisations

If a subject is admitted to hospital this is considered to constitute a serious adverse event and as such a 'serious adverse event' form is completed. The only exceptions to this are hospital admissions that are pre-planned for elective procedures eg, laser eye surgery, PEG replacement, and cosmetic procedures. "Hospital in the home" or an equivalent program is not considered to be a hospital admission. Medications administered as part of any elective procedure or hospital

in the home process, are to be recorded as concomitant medications.

3.3.18.1 Hospital Admission

At the time of hospital admission, the following information will be recorded if available:

- physical examination and medical history
- signs and symptoms checklist
- sputum microbiology results
- spirometry
- number of days since last hospital admission
- results of laboratory tests
- chest x ray report

3.3.18.2 Hospital Discharge

In addition to information recorded as per hospital admission, at the time of hospital discharge the following information must be obtained as close as possible to the discharge date.

- medications during admission
- number of days in hospital

3.3.19 Health Care Costs

A standard costing method will be used to assess the total health care cost from a community-health-service and hospital perspective. Subject's personal costs will be excluded. Included in the assessment will be: hospital admissions (inpatient, outpatient, day case); radiological investigations, blood tests, medication use, and the use of community services (eg visits to general practitioners, district nurses and physiotherapists). Resources will be recorded from medical records, discharge summaries and subjects' diaries. Unit costs will be obtained from finance departments at the hospitals involved in the study and a district general hospital. Costs will include health professionals' time, consumables and overheads. Medication costs will be taken from documents such as *British National Formulary* and the Australian *Pharmaceutical Benefits Schedule* or as nationally appropriate for other countries, and community care costs from published data. Total hospital and community costs will be calculated by multiplying resource use by unit costs.

3.3.20 Study Drug Administration Procedure

Subjects should be taught how to administer the study medication as follows:

- Pre-medicate with the same bronchodilator and dose used for pre-medication during the Aridol-MTT procedure. Salbutamol 4x 100µg is the study bronchodilator of choice.
- Wait 5 - 15 minutes
- Insert capsule into the Osmohaler HR device
- Puncture the capsule by pressing the side buttons **once** only (a second puncture may shatter the capsule).
- Exhale (away from device),
- Place mouthpiece between teeth, create a firm seal with lips, then inhale from the device in a deep, controlled manner being sure to invoke capsule 'rattling' in the device
- Breath hold for 5 seconds before exhaling away from device. It is okay to take a second

inhalation to ensure complete emptying.

- Remove the empty capsule from device.
- Load the next capsule, puncture and inhale as above. One capsule should follow the previous capsule immediately, so the osmotic effect is cumulative.
- Repeat until prescribed number of capsules has been inhaled completely.
- Problematic cough may be controlled by slowing the rate of inhalation.
- Wash residual study medication from the mouth and throat by drinking water.
- Keep the empty blister for drug accountability.

Subjects will be given bronchodilator to take home to be used as pre-medication before every study treatment. They may also be used in the event that they experience chest tightness post treatment. The pharmacist is responsible for dispensing the bronchodilator. The investigator is responsible for instructing the subject in the use of the bronchodilator inhaler. Alternative bronchodilator may be used if the subject does not tolerate salbutamol.

Treatments are to be taken twice a day, once in the morning and once in the evening, approximately 2 hours before sleep and ideally within 30 minutes before the subject's regular treatments and physiotherapy session. An adequate supply of devices will be given to the subject. If the subject is unable to attend for follow up assessment on due visit date, additional blisters have been included in each supply to allow for a delay of 14 days in each study period. Subjects should attend for assessment before the last treatment is used. Subjects should bring in all used and unused blisters at each assessment visit to check for compliance.

Study medication must not be refrigerated nor kept in humid conditions such as bathrooms. It should be stored at room temperature in a clean, dry environment. Capsules should only be removed from the foil packaging just prior to use.

3.3.21 Administration of Treatment Dose in Clinic at Visit 1, 3 and 4

Applies to visit 1, 3 and 4

The study staff will administer the visit 1, visit 3 and visit 4 dose of study medication in the clinic according to the following plan:

(V1 and V4 only. Administer the treatment dose following the bronchodilator response test to avoid duplication of some procedures)

1. Verify medication washout periods (see Table 1, Section 3.3.7.1)
2. Perform pre-bronchodilator spirometry
3. Administer 4 x 100 µg salbutamol. Alternative bronchodilators may be used if patient preferred. Wait 5 minutes then perform post bronchodilator FEV_1.
4. Administer dose of prescribed study medication as described in 3.3.20
5. Collect ALL sputum produced during the procedure into a pre-weighed specimen jar. The entire sample collected during and for 30 mins post dose will be weighed and recorded. This sputum collection applies to Visit 1 and 3 only.
6. Measure FEV_1 30 minutes post dose completion.

If a subject has a measured fall in FEV_1 $\geq$20% at 30 minutes post dose completion, no further study medication should be administered. The subject should be continued in the study on an

intention to treat basis. Symptomatic bronchoconstriction should be managed as medically appropriate.

3.3.22 Forced Oscillation Technique

Applies to visits 1, 2, 3 and 4

Participating sites: Papworth Hospital Cambridge UK and Royal Children's Hospital, Melbourne Australia.

Background

Conventional techniques for assessing the presence and severity of airway obstruction and changes with an intervention include spirometry (FEV_1, FEF_{25-75}). Forced Oscillation Technique (FOT) measures the impedance of the respiratory system and it can be a more sensitive technique compared to spirometry for assessing airway obstruction and the effect of an intervention in the airways and in particular in the small airways. FOT uses 'forced' pressure oscillations generated by a loudspeaker to measure the impedance of the respiratory system at multiple frequencies (5-35 Hz). Respiratory impedance is a complex quantity and includes both resistance (Rrs) and reactance (Xrs). Proximal airways obstruction would increase Rrs evenly at all frequencies. By contrast, in distal airways obstruction, Rrs is frequency dependent with the highest value at low frequency. Reactance is also a complex quantity itself and incorporates the inertial and elastic forces of the lung. Reactance at low frequencies (capacitative Xrs) is negative and relates to the elastic forces while at high frequencies (inertive Xrs) it is positive and relates to the inertial forces of the lung. The frequency at which the capacitative and inertive Xrs are equal is defined as the resonant frequency (Fres). Reactance area (AX) is a quantitative index of the total reactance at all frequencies between 5 Hz and Fres. FOT is particularly sensitive for assessing peripheral airways obstruction.

The aim is to measure resistance and reactance before and after treatment with IDPM/control in order to assess changes due to clearance of mucus in patients with significant small airways obstruction and mucus retention. Excessive airway mucus can potentially obstruct the airways if it is not cleared. Previous studies of patients with bronchiectasis found that a 2 week treatment with IDPM showed a significant improvement in the low frequency reactance. This suggested changes in the small airways after effective clearance of mucus with IDPM treatment.
We hope to demonstrate improvement in resistance, reactance, resonant frequency and reactance area.

Procedure

The pressure oscillation signals are superimposed on the spontaneous breathing of the subject and do not require specific respiratory manoeuvres. The subject breathes quietly through an airtight mouthpiece for 30-40s. Measurements are repeated twice and the mean value is reported.

Analyses

Comparison of the pre treatment with the post treatment values using ANOVA with repeated measures. In particular the comparison will be of the following parameters:

- Resistance at high frequency (large airways): R25, Rin25;
- Resistance at low frequency (includes both large and small airways): R5, Rin5;
- Frequency depending resistances: R5-R15, R5-R20, Rin5-Rin15, Rin5-Rin20;
- Resonant frequency: Fres and Fresin;
- Reactance at low frequency: X5, X5in
- Slope of Reactance at high frequencies: X35/(35-Fres), Xin35/(35-Fresin) and X25/(25-Fres), Xin25/(25-Fresin)
- Reactance Area: AX, Axin

References

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Smith HJ, Reinhold P, Goldman MD. Forced oscillation technique and impulse oscillometry. In Lung Function Testing ed R Gosslink and H Stan. *European Respiratory Monograph, 2005; Vol 10, Monograph 31,pp 72-105.*

Goldman, M. D., E. Daviskas, J. A. Turton, and S. D. Anderson. 2004. Inhaled mannitol improves lung function assessed by Forced Oscillation in a placebo controlled trial in patients with bronchiectasis. *Eur Respir J; 24(Suppl 48): 470.*

3.4 Open Label Periods

The purpose of the open label periods are to obtain data on the long term safety and tolerability of IDPM and to give those subjects randomised to the control arm exposure to the active treatment. This component will be analysed separately to the initial 26 week treatment study. Subjects consenting for the 1st open label period will receive active treatment for an additional 26 weeks. On completion, a 2nd open label period will be offered to subjects for an additional 26 weeks to provide a total exposure of 12 to 18 months on active medication.

At visits 4 and 6, subjects have the option of continuing on the study medication for an additional 26 weeks providing:

1) the subject has consented and wishes to continue on study medication

2) the investigator does not believe there are any clinical reasons to withdraw the subject from treatment

3) the subject is not pregnant or planning to become pregnant in the next 6 months

3.5 Time Schedule and Accrual Procedures

Subject accrual is expected to occur at an average rate of 1 subject every month per centre. Subject enrolment will end when recruitment goals are met unless the study is terminated early or attrition rates are beyond expected, whereby the recruitment period will be extended. These accrual rates are based on retrospective data provided by the investigator(s), i.e., on the number of subjects who would have satisfied the proposed inclusion/exclusion criteria in the past. The investigator(s) should make every effort to ensure that the planned accrual rate is maintained, that eCRFs are completed promptly and completely, and that data quality is maintained at all times. The investigator(s) should discuss with the monitor any anticipated problems with recruitment or delays in study completion.

3.6 Randomisation and Blinding

Any subject giving consent, but not fulfilling the criteria to participate in the study, will not receive an enrolment number; however, data collected at screening may be recorded using the subject's initials and date of birth as identifiers.

No treatment will be assigned to a subject before the subject has given consent and it has been ascertained that the subject has met all inclusion and exclusion criteria. An enrolment number will then be assigned to the subject such that all subjects from a centre are given consecutive enrolment numbers in successive order of inclusion. Enrolment numbers will be generated electronically when the subject's data is entered into the eCRF. The enrolment number will correlate to one of 2 randomisation schedules. The randomisation schedules will be independently generated in blocks of five, for a parallel study design and stratified according to region and RhDNase use. For every 3 subjects randomised to active treatments, 2 subjects will be allocated to control.

Assignment of Treatment Sequences

The treatment will be allocated to eligible subjects according to the randomisation schedule.
The Sponsor is responsible for preparing the allocation prior to shipping.
The Sponsor will ship the subject's treatment allocation, identifiable by the enrolment number, and batch number to the pharmacist, along with the sealed randomisation code break.
The pharmacist will dispense the treatment allocated to the subject and record the batch number and enrolment number in the dispensing log.

Note that subjects will be included if there are any mismatches in randomisation selection and treatment dispensing - but careful consideration will be given to the number of cases and effect of this on the findings.

Both the subject and the investigative staff will be blinded to the treatment allocations. Sealed randomisation envelopes will be kept with the study pharmacist and will only be made available to the principle investigator in the event of a serious adverse event requiring unblinding or an emergency. Pharmaxis must be consulted before any randomisation code is broken.

During the open label phase all eligible subjects will receive 26 weeks of active medication.

3.7 Investigational Product

IDPM /control capsules are packaged in blisters and come with a dry powder inhaler device for every 7 days supply. Empty blister packaging and unused blisters will be returned for compliance checks. Subjects will inhale the contents of the prescribed number of capsules twice a day before physiotherapy/exercise. IDPM/control must be stored and dispensed by the pharmacist.

3.8 Study Treatment and Dosage

IDPM/control: To be administered in the following regimens.
Visit 0: Subjects who pass all inclusion/exclusion criteria are randomised to one of the following arms:

400 mg or control BD

Ratio	Dose	Duration	1st Open Label Period	2nd Open Label Period
3	IDPM 10 caps BD	26 weeks	IDPM 10 caps BD for 26 weeks	IDPM 10 caps BD for 26 weeks
2	Control 10 caps BD	26 weeks		

3.9 Duration of Subject Participation

The total study duration for each participant will be 28 (blinded phase) or 54 weeks (1st open label phase) or 78 weeks (2nd open label phase). Subjects consenting for the 1st open label phase will all receive active treatment for an additional 26 weeks. Subjects consenting for the 2nd open label phase will all receive active treatment for an additional 26 weeks (total open label 52 weeks).

3.10 Stopping Rules and Discontinuation Criteria

Once enrolled, subjects will be discontinued from the study in the following circumstances:

- Subject withdraws consent
- The Investigator decides that the subject should be withdrawn. If this decision is because of a serious adverse event, further administration of the study drug should be ceased and appropriate measures taken. The Sponsor (representative) and the institutional ethics committee are to be notified immediately
- The subject's attending physician requests that the subject be withdrawn from the study
- The Investigator or the Sponsor, for any reason, stops the study or stops the subject's participation in the study
- The subject is inadvertently enrolled but does not meet the enrolment criteria
- Pregnancy
- Non compliance with study medication or poor visit attendance
- Concurrent use of hypertonic saline or beta blockers
- Subjects who experience an FEV_1 fall of $\geq$50% post IDPM/control, should be continued in the study on an intention to treat basis. However they should not receive further study medication.

3.11 Study Drug Supply and Accountability

Each Investigator is responsible for ensuring that deliveries of study drug(s) and other study materials from the Sponsor are correctly received and recorded, that these materials are handled and stored safely and properly, and that they are used in accordance with this protocol.

Unused study drug(s) (opened, unopened, or empty blisters) must either be returned to the Sponsor or destroyed on site only after any discrepancies have been investigated and satisfactorily explained and fully reconciled by the Sponsor. Approval to destroy drug must be given in writing by the Sponsor prior to destruction. A list of study drug(s) and other materials received, used, returned, or destroyed must be prepared and signed by the Principal Investigator;

and an account must be given for any discrepancies. The site pharmacy will be responsible for storage and dispensing of the IDPM/control. All investigational drugs must be accounted for at the beginning, during and at completion of the study. The site Pharmacy will be supplied with an instructional study manual.

3.12 Source Data and the Case Report Form

In this study the case report form will be an electronic Case Report Form (eCRF), built on an electronic data capture platform. The eCRF is compliant with 21 CFR Part 11. It has full technical support for electronic signatures and contains all functionality required for electronic records retention. The database (including full audit trail, eCRF and user data) and all versions of the software will be retained to ensure data is accessible at later dates and each site will receive a copy of their own data for long term archival. The eCRF will display identification numbers corresponding to the number of the centre and the subject enrolment number.

A full identification list of each participant will be kept by the Investigator who must agree to supply all details to Sponsor auditor(s) and/or regulatory authorities if required. The information will be treated in compliance with professional confidence and government regulations.

The Investigator or the designated site person must agree to complete the eCRF at each subject visit, and all other documents provided by the Sponsor. All corrections and alterations of data on the eCRF must be made by the Investigator or by the designated site person according to the instructions provided. All persons appointed by the Investigator to participate in the study must be indicated on the delegation of authority log.

Each Investigator or site designee will be assigned a unique user name and password. The user name and password combination will be used to sign the eCRF at each visit, attesting to the authenticity of the data collected in the case report form and agreement between the data in the case report form and those in the source documents. Access will be restricted in compliance with 21 CFR Part 11.

In the case of withdrawal of consent or early termination by a participant, the Investigator or Co-Investigator will complete the study completion/withdrawal page, indicating the reason for early termination. Study completion will be signed electronically. The entry of the Investigator or sub-investigator's user name and password combination will be considered the equivalent of a written signature. The following statement will appear with the electronic signature: "I affirm by my electronic signature above that I have reviewed all of the information on all pages/forms of this case report form and assume responsibility for the accuracy and completeness of the data."

The study will be monitored to ensure that all data are completed accurately on the eCRF as can be determined by a monitor at the site. Requests for correction/clarification will be submitted to the Investigator by the monitor or data manager when inconsistencies are identified during monitoring and source data verification or during the edit check and data review process. The Investigator or designee will make the corrections in the system and submit the eCRF pages once again. The monitor or data manager will approve the corrections made in the system.

Any data recorded directly on the eCRF, for which no other written or electronic record exists in the subject's medical record, will be considered source data (e.g. results of physical examinations, vital signs testing, or the drug administration procedure) and will be provided to the site in an electronic format at the end of the study.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Number of Subjects and Target Population

A minimum of 340 evaluable subjects are required to be randomised. Subjects will have a diagnosis of cystic fibrosis, be aged $\geq$ 6 years, with a baseline FEV_1 $\geq$30% and <90% predicted, not be pregnant or breast feeding, will not have an intolerance to mannitol or beta agonists. There will be no concurrent use of hypertonic saline or beta blockers. Subjects must be Aridol-MTT negative to be eligible for randomisation.

4.2 Subject Inclusion Criteria

Subjects may be included in the study if all of the following criteria are met. The subject must:

1. Have given written informed consent to participate in this study in accordance with local regulations
2. Have a confirmed diagnosis of cystic fibrosis
3. Be aged $\geq$ 6 years
4. Have FEV_1 $\geq$30 % and < 90% predicted
5. Be able to perform all the techniques necessary to measure lung function

4.3 Subject Exclusion Criteria

Subjects are excluded from participating in this study if one or more of the following criteria are met. The subject must NOT:

1. Be investigators, site personnel directly affiliated with this study, or their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biologically or legally adopted.
2. Be considered "terminally ill" or listed for lung transplantation
3. Have had a lung transplant
4. Be using nebulised hypertonic saline
5. Have had a significant episode of haemoptysis (>60 mL) in the three months prior to enrolment
6. Have had a myocardial infarction in the three months prior to enrolment
7. Have had a cerebral vascular accident in the three months prior to enrolment
8. Have had major ocular surgery in the three months prior to enrolment
9. Have had major abdominal, chest or brain surgery in the three months prior to enrolment
10. Have a known cerebral, aortic or abdominal aneurysm
11. Be breast feeding or pregnant, or plan to become pregnant while in the study
12. Be using an unreliable form of contraception (female subjects at risk of pregnancy only)
13. Be participating in another investigative drug study, parallel to, or within 4 weeks of study entry
14. Have a known allergy to mannitol
15. Be using beta blockers
16. Have uncontrolled hypertension – systolic BP > 190 and / or diastolic BP > 100
17. Have a condition or be in a situation which in the Investigator's opinion may put the subject at significant risk, may confound results or may interfere significantly with the patient's participation in the study
18. Be 'Aridol-MTT test positive'. (As evaluated in section 3.3.8.5)

4.4 Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki, each subject has the right to withdraw from the study at any time without prejudice. An Investigator also has the right to withdraw subjects from the study in the event of intercurrent illness, AEs or other reasons concerning the health or well being of the subject. The Investigator also has the right to withdraw subjects in the case of lack of compliance.

Should a subject decide to withdraw after administration of study drug(s), or should the Investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason and date for withdrawal must be noted on the eCRF. If the reason for withdrawal is an AE or an abnormal laboratory test result, monitoring will continue until resolution or until an appropriate medical judgment concerning the cause or importance has been made. The specific event or test result(s) must be recorded on the eCRF.

5 TREATMENT OF SUBJECTS

5.1 Treatments Administered and Instructions for Use

5.1.1 Concurrent Medications RhDNase

Subjects that are using RhDNase routinely prior to enrolment in this clinical trial should continue to use RhDNase throughout the trial. Wherever possible RhDNase treatment should be kept consistent throughout the study period. If RhDNase is commenced or ceased, or the treatment schedule is changed during the study, this should be noted in the concomitant medications. A record that reflects **actual** RhDNase use, rather than prescribed use, should be maintained.

5.1.2 Study Medication

All subjects are required to take bronchodilator at least 5 minutes prior to inhalation of the study medication. They should use the same bronchodilator and dose that was administered at the Aridol-MTT procedure. Additional bronchodilator may be used in the event of wheeze, dyspnoea and chest tightness. Such use should be recorded.

IDPM/control: To be administered as either 400 mg IDPM or control BD. In the blinded phase, eligible subjects are randomised in a 3: 2 ratio (active to control), while in the open label phase, all subjects will receive 400mg IDPM BD, as below:

Ratio	Blinded Phase	Duration	1st Open Label Phase	2nd Open Label Phase
3	IDPM (10 caps BD)	26 weeks	IDPM 10 caps BD for 26 weeks	IDPM 10 caps BD for 26 weeks
2	Control (10 caps BD)	26 weeks		

Capsules are administered using a high resistance dry powder inhaler device (Osmohaler HR).

5.2 Prohibited Medications During the Study

Nebulised hypertonic saline (HS) (confounds study results). Any subject using HS at screening who is deemed to be eligible for the study on all other criteria and who wishes to participate in the study, should cease further HS use at screening. A 4 week HS washout period should then occur between screening and visit 1. There is no requirement to cease rhDNase.
Beta blockers (may interfere with $beta_2$ agonists)

5.3 Order of Daily Procedures During the Study

The recommended order of treatment procedures is:

1. bronchodilator
2. IDPM/control
3. physiotherapy / exercise
4. RhDNase
5. inhaled antibiotics
6. inhaled cortico-steroids

The procedures 4, 5 and 6 may not be applicable to all subjects and the order of points 3, 4, 5 and 6 listed above is a suggestion only.

5.4 Medications and Physiotherapy on Study Visit Days

Refer to Table 1 in section 3.3.7.1 for withholding times for respiratory medications prior to conducting spirometry.

The last dose of IDPM/control and associated physiotherapy should be taken approximately 12 hours prior to study visit. This will ensure that the subject is near to the trough in dose response and acute medication effects have worn off.

So accurate measures of trough spirometry can be made, the treatment routine on visit days is imperative, therefore administration of respiratory medications and physiotherapy should be identical on these days and the time of day for the visit should be as close as practical.

5.5 Rescue Medications

If a subject develops chest tightness or shortness of breath as a consequence of withholding bronchodilators or other respiratory medications on the morning of the visits, they should take a short acting bronchodilator (rather than long acting) and phone the clinic to reschedule the visit for as soon as possible, ensuring that study schedules are maintained. All subjects will be issued bronchodilator for the duration of the study.

6 ASSESSMENT OF EFFICACY

6.1 Primary and Secondary Endpoints

6.1.1 Primary Endpoints:

- Change in absolute FEV_1

6.1.2 Secondary Endpoints:

- Change in absolute FEV_1(RhDNase group)
- Pulmonary exacerbations in those taking RhDNase as a sub-group and in the total cohort
- Quality of Life Scores using Cystic Fibrosis Questionnaire
- Rescue antibiotic use (number of agents course and days of use)
- Change in FVC, FEF_{25-75} from baseline
- Days in hospital due to pulmonary exacerbations
- Cost effectiveness including total costs of hospital and community care
- Safety

7 ASSESSMENT OF SAFETY

7.1 Safety

Safety will be assessed by tracking the number and percentage of adverse events at 6, 12 and 18 months. In addition subjects will be monitored for changes in haematology, liver and renal function. Sputum will be examined for pathogens at each visit and this will be compared between groups and to baseline. A bronchodilator response test will be conducted at baseline and after 26 weeks of treatment.

7.2 Procedures for Adverse Events and Intercurrent Illnesses

The appropriate clinical staff at the study site will handle any medical emergencies involving trial subjects.

For purposes of collecting and evaluating all information about Pharmaxis drugs used in clinical trials, a clinical trial adverse event (AE) is any unfavourable or unintended change in the structure, function or chemistry of the body, temporally associated with the use of a Pharmaxis product, whether or not considered to be related to the product. Any worsening (e.g. clinically significant adverse change in frequency and/or intensity) of a pre-existing condition, which is temporally associated with the use of a Pharmaxis product, is also an AE.

Changes resulting from normal growth and development, which do not vary significantly in frequency or severity from expected levels, are not to be considered AEs. Examples of this may include, but are not limited to: teething, period pain, typical crying in infants and children, bedwetting, the onset of menses or menopause occurring at a physiologically appropriate time.

Planned hospital admissions for pre-existing conditions are not considered to be adverse events.

Bronchoconstriction is an expected effect during the Aridol-MTT procedure and is not to be considered an adverse event unless the bronchoconstriction causes a $\geq$50% fall in FEV_1 or the subject desaturates to $\leq$89%.

If at any other time during or immediately following the administration of the IDPM/control powder, the subject experiences a fall in FEV_1 of $\geq$20% due to bronchoconstriction, the subject should be monitored for 30 minutes before having the FEV_1 measurement repeated. Subjects who have not recovered their FEV_1 to <20%, at this point and provisos 1 and 2 (below) have been met, should not receive further study medication.
1) a suitable bronchodilator was taken prior to administration of the IDPM/control;
2) the investigator determines that the fall in FEV_1 is bronchoconstriction and not due to mucus plug or floppy airway collapse. This can be tested by administering positive pressure via a PEP mask or Acapella device or similar and repeating the FEV_1 manoeuvre.

If the fall in FEV_1 persists below 20% subjects should discontinue study medication but should be encouraged to continue in the study and undergo all study procedures (that do not require administration of IDPM/control) as scheduled up until the end of visit 4 when the base study is deemed to be complete.

7.3 Adverse Events Recording Requirements

Baseline Evaluation

At screening, the Investigator will record a full medical history and any medications used by the subject to treat such conditions. Recurring symptoms associated with pre-existing conditions will not be considered AEs during the study, unless they have a *clinically significant increase in severity and/or frequency*. Out of range laboratory results at screening will be recorded as pre-existing conditions. If a pre-existing condition is discovered during the study, but not recorded at screening, a correction to the study record should be made.

Prior to enrolment, study site personnel will evaluate and record the subject's medical condition(s). During the study, site personnel will evaluate and record any change in the condition(s) and/or the occurrence of any AEs.

Study Evaluations

Subjects and/or parents/caregivers (if appropriate) will be questioned for the occurrence of any new or worsening signs or symptoms at each visit. Out of range laboratory results arising once study medication has begun, will be reviewed and signed by the investigator. The Investigator will determine whether the signs and symptoms represent clinically significant changes from the subject's baseline condition, and if so, they should be recorded as an AE.

- During the study and for 7 days post study completion/withdrawal, all AEs will be followed until resolution or until an appropriate medical judgment concerning the cause or importance has been made.

- AEs may also occur in screened subjects during any pre allocation baseline period as a result of a protocol-specified intervention. Such AEs will be recorded.

The Investigator will evaluate all AEs as to:

- Seriousness: See Serious Adverse Events section

- Severity
  - Mild (awareness of sign or symptom but easily tolerated)
  - Moderate (discomfort causes interference with usual activity)
  - Severe (incapacitating, or unable to do usual activities)

- Duration: Record the onset and stop dates of the event. If less than one day, record the appropriate length of time and units

- Action taken: Did the event cause the study drug or procedures to be discontinued or postponed?

- Relationship to study drug: Did the study drug cause the AE? The likelihood that the study drug caused the AE must be determined by the **physician Investigator.** The

following criteria should be used to assist the physician Investigator to determine causality between the AE and the study drug:

Exposure:

- Is there evidence to show that the subject was exposed to the drug such as reliable history, acceptable compliance assessment (capsule count, etc.), expected pharmacological effect, or measurement of drug/metabolite in bodily specimen?

Time Course:

- Was there a reasonable time sequence between exposure and AE?
- Is the time of onset of AE compatible with a drug induced effect?

Likely Cause:

- Can the AE be reasonably explained by other aetiology such as underlying disease, other drug(s), or other host environmental factors?

Dechallenge:

- Was the dose of test drug discontinued or reduced?
  - If yes, did the AE resolve or improve?
  - If yes, this is a positive dechallenge
  - If no, this is a negative dechallenge

  Note: This criterion is not applicable if:
  1. the AE resulted in death or permanent disability
  2. the AE resolved/improved despite continuation of the test drug
  3. the study is a single dose study
  4. the AE occurred after the last study dose

Rechallenge:

- Was the subject re-exposed to the test drug in this study?
  - If yes, did the AE recur or worsen?
  - If yes, this is a positive rechallenge
  - If no, this is a negative rechallenge

  Note: This criterion is not applicable if:
  1. the AE resulted in death or permanent disability
  2. the study is a single dose study
  3. the AE occurred after the last study dose

Note: If a rechallenge is planned for an AE which was serious and which may have been caused by the study drug, or if re-exposure to the study drug poses additional potential significant risk to the subject, then the rechallenge must be approved in advance by the medical monitor and the local institutional ethics committee.

Consistency with study drug profile:

- Is the clinical presentation/pathology consistent with previous knowledge regarding the study drug or drug class pharmacology or toxicology?

The assessment of relationship will be reported by the Investigator according to his/her best judgment, including consideration of the above elements. Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a drug relationship):

Definitely related to study drug:

- There is evidence of exposure to the study drug
- The temporal sequence of the AE onset relative to administration of the test drug is reasonable
- The AE is more likely explained by the test drug than by another cause
- Dechallenge is positive
- Rechallenge (if feasible) is positive
- The AE shows a pattern consistent with previous knowledge of the test drug or test drug class

Probably related to study drug:

- There is evidence of exposure to the study drug
- The temporal sequence of the AE onset relative to administration of the test drug is reasonable
- The AE is more likely explained by the test drug rather than by another cause
- Dechallenge (if performed) is positive

Possibly related to study drug:

- There is evidence of exposure to the study drug
- The temporal sequence of the AE onset relative to administration of the test drug is reasonable
- The AE could have been due to another equally likely cause
- Dechallenge (if performed) is negative or ambiguous
- Rechallenge (if performed) is negative or ambiguous

Probably not related to study drug:

- There is evidence of exposure to the study drug
- There is another more likely cause of the AE.
- Dechallenge (if performed) is negative or ambiguous
- Rechallenge (if performed) is negative or ambiguous

Definitely not related to study drug:

- The subject did not receive the study drug OR
- Temporal sequence of the AE onset relative to administration of the study drug is not reasonable OR
- There is another obvious cause of the AE

An AE that later meets the criteria for a serious adverse event (SAE) within the study period must be reported as a serious adverse event. After the study period, only if a serious adverse event is believed to be related to the study drug administration should it be reported.

7.4 Serious Adverse Events

A serious adverse event for this study is defined as any unfavourable medical occurrence that:

1. Results in the **death** of the participant

2. Is **life-threatening**
   - the term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe

Eg: Pacemaker failure; gastrointestinal haemorrhage; bone marrow suppression; infusion pump failure, which permits uncontrolled free flow resulting in excessive drug dosing

3. Requires **inpatient hospitalisation** or prolongation of existing hospitalisation
   - hospitalisation is defined as inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation
   - hospitalisation for a pre-existing condition which has not worsened, including/or hospitalisation for an elective procedure, does not constitute a serious adverse event.
   - 'hospital in the home' or its regional equivalent, is not to be considered an inpatient hospitalisation and therefore does not constitute a serious adverse event.

Eg: Anaphylaxis; pseudomembranous colitis; or bleeding causing or prolonging hospitalisation

4. Results in persistent or significant **disability** or incapacity

Eg: Cerebrovascular accident due to drug induced hypercoagulability; toxicity; peripheral neuropathy

5. Is a **congenital anomaly** or birth defect

Eg: Vaginal cancer in female offspring from diethylstilbestrol during pregnancy; malformation in the offspring caused by thalidomide

6. Is an **important medical event**
   - any event which is not immediately life-threatening and does not result in death or hospitalisation but which may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed above

Examples: Paracetamol overdose induced hepatotoxicity requiring treatment with acetylcysteine to prevent permanent damage; burns from radiation equipment requiring drug therapy; breakage of a screw requiring replacement of hardware to prevent malunion of a fractured long bone.

Immediately upon notification of the occurrence of any serious adverse event, the Principal Investigator or designee must contact the study clinical research associate and Pharmaxis by fax +61 2 9454 7255 and email (refer to contacts list).

Serious adverse events must be reported to Pharmaxis within 24 hours of notification of the occurrence.

The site will complete the Serious Adverse Event Form with as much detail as possible. The site will fax this form to the study CRA. All AEs must be reported in the case report form.

The Investigator is responsible for an assessment of causality, intensity, and relationship to study treatment. Actions taken and outcomes must also be recorded. All AEs and serious adverse events will be followed until an appropriate medical judgment concerning the cause or importance has been made. The Sponsor is responsible for reporting adverse events to the relevant governing authorities in the time frames and methodology applicable according to local law.

7.5 Data Safety Monitoring Board

This data safety component of this study will be conducted by the Cystic Fibrosis Foundation Data Safety Monitoring Board whose offices are located in Tucson, Arizona, USA. The primary responsibility of the DSMB is to protect the safety and welfare of patients participating in this clinical trial and to ensure the integrity of the study. The DSMB will comprise of a Data Monitoring Committee (DMC) which will review clinical data relating to safety and efficacy and ensure the continued scientific validity and merit of the study.

DSMB duties:

- Reviewing significant adverse events and adverse event trends
- Examining accumulated outcome and safety data in order to make recommendations concerning continuation, termination or modification of the trial based on the effects of the interventions under study
- Reviewing major study design modifications proposed by the sponsor prior to implementation
- Reviewing the general progress of the studies with regard to accrual, protocol violations, and study conduct

The DSMB will receive SAEs in real time as well as periodic safety reports, therefore facilitating a response to potential safety issues. The DSMB will also receive one report for the purposes of an interim analysis. The web based data capture system is programmed to produce regular reports of study progress and conduct and other requirements as deemed necessary.

8 STATISTICS

8.1 Objectives

Primary Objective:

- To determine the effect of IDPM compared to control on FEV_1 in all patients with CF

Secondary Objectives

- To determine the effect of IDPM compared to control on FEV_1 in patients with CF on existing RhDNase treatment. (key objective)
- To assess whether IDPM treatment:
  - Reduces pulmonary exacerbations in those taking RhDNase as a sub-group and in the total cohort (key objective)
  - Improves quality of life (key objective)
  - Reduces days on IV antibiotics
  - Reduces days on rescue oral or inhaled antibiotics
  - Reduces days in hospital due to pulmonary exacerbations
  - Improves other measures of lung function
  - Demonstrates an appropriate safety profile (adverse events, haematology, biochemistry, change in bronchodilator response, sputum microbiology, physical examination)
  - Reduces hospital and community care costs

8.2 Efficacy and Safety Outcome Measures

Primary Outcome Measures

- Change in absolute FEV_1

Descriptive analysis will show the change from baseline in FEV_1. Descriptive statistics will include the mean change, the standard deviation, the median change, the minimum change and the maximum change, at each of the post baseline FEV_1 assessments (weeks 6, 14 and 26).

Inferential analysis will involve a repeated measures analysis of the change in FEV_1 from baseline, taking age, disease severity at baseline, and baseline FEV_1 as covariates for each patient. Dry powder mannitol dose will be categorised at two levels in order to assess dose response: Control and 400mg. The model will take the form:

$$\text{change in } FEV_1 \text{ from baseline} = \text{dose} + \text{week} + \text{dose*week} + \text{age} + \text{disease severity} + \text{baseline } FEV_1.$$

Patient number will also be specified as a random effect in the model. The treatment effect of 400mg of dry powder mannitol will be estimated by the value of the dose coefficient from the model. The interaction of dose and time (Study Week) will also be reported in order to examine changes in effect over the course of the initial 26 week study period. Least squares mean values and standard errors for the change from baseline in FEV_1 at each post-baseline assessment, by dose level, will be presented in tables and also as a graph.

Secondary Outcome Measures

- Change in absolute FEV_1 (RhDNase group)

The descriptive analysis will be the same as described for the primary efficacy outcome measure.

- Pulmonary exacerbations (as defined)

The number and percentage of patients experiencing at least one pulmonary exacerbation event in the initial 26 week study period will be presented by dose level (control and 400mg).

Pulmonary exacerbation rates for each dose level in the first 26 week study period will be compared using Poisson regression analysis. Age and baseline disease severity will be used as covariates for each patient. The model will take the following form:

number of exacerbation events = dose + age + disease severity.

The number of days on Study in the initial 26 week period will be included in the model as an offset, thereby adjusting for differing lengths of exposure on study for different patients. Rates will be expressed as the number of events per person year of observation. 95% confidence intervals for the rates will be shown. The rate ratios comparing dry-powder mannitol 400mg to the control will be presented. 95% confidence intervals for the rate ratio will be shown. This analysis will be undertaken on the safety population. The analysis will also be repeated for exacerbations in the open label period.

- Quality of Life Scores using Cystic Fibrosis Questionnaire

Component questions in the questionnaire will be appropriately transformed so that the best response is uniformly the highest score, and the worst response is uniformly the lowest score. The total will be the sum of the component question responses. At each visit, descriptive statistics (mean, standard deviation, median, minimum and maximum scores) will be presented by dose level (control and 400mg). Also, at weeks 14, and 26, change from baseline scores will be presented using the same descriptive statistics. Inferential analysis will be performed in a similar manner to that of the primary endpoint.

- Rescue antibiotic use (number of agents, course and days of use)

Rescue antibiotics used during the first 26 weeks of treatment will be displayed individually for each patient. Additionally, a summary tabulation of rescue agent showing the number of uses will be shown by dose level (control and 400mg). The number and percentage of patients with no rescue antibiotic use, and 1, 2, 3 and >3 distinct episodes of rescue antibiotic use will also be shown. The average number of days of use of rescue antibiotics will also be tabulated by dose level (for both the safety population, and the subset of the safety population that required at least one rescue antibiotic in the first 26 week period). The standard deviation, median, minimum and

maximum number of days of rescue antibiotic use will also be shown. Exposure to rescue antibiotics will also be estimated. Exposure to rescue antibiotics will be expressed as the number of day's use of rescue antibiotics per person year of observation. Data will be analysed using Poisson regression as described for pulmonary exacerbations. If the data for rescue antibiotic use displays evidence of over dispersion in the Poisson regression analysis, a similar model using the negative binomial distribution will be used to analyse the data.

This analysis will be undertaken on the safety population. The analysis will also be repeated for rescue antibiotic use in the open label phase.

- Change in FVC, FEF_{25-75} from baseline

These data will be analysed using similar techniques to those described for the primary efficacy outcome measure. Analysis will be undertaken on both the ITT and PP populations.

- Days in hospital due to pulmonary exacerbations

Days in hospital due to pulmonary exacerbations used during the first 26 weeks of treatment will be displayed individually for each patient. The number and percentage of patients with no days in hospital, and 1, 2, 3 and >3 days in hospital (across all hospitalisation events) will also be shown by dose level (control and 400mg). The average number of days in hospital will also be tabulated by dose level (for both the safety population, and the subset of the safety population that required at least one day in hospital due to pulmonary exacerbations in the first 26 week period). The standard deviation, median, minimum and maximum number of days in hospital will also be shown.

The rate of hospitalisation due to pulmonary exacerbations in the first 26 week study period will also be estimated. Hospitalisation rates will be expressed as the number of days of hospitalisation per person year of observation. Data will be analysed using Poisson regression as described for pulmonary exacerbations. If the data for days in hospital displays evidence of over dispersion in the Poisson regression analysis, a similar model using the negative binomial distribution will be used to analyse the data.

This analysis will be undertaken on the safety population. The analysis will also be repeated for days in hospital due to pulmonary exacerbations in the open label phase.

Measures of Safety

- Adverse events

The number and percentage of patients experiencing adverse events will be tabulated. Additional summary data will be presented for:

- serious adverse events,
- treatment related adverse events (defined as being possibly, probably or definitely related to treatment in the opinion of the investigator),
- treatment related serious adverse events,
- adverse events leading to study withdrawal,
- treatment related adverse events leading to study withdrawal, and

- deaths.

In addition, adverse events will be summarised by MedDRA system organ class and preferred term. Each of these analyses will be conducted at the patient level, that is, multiple adverse events within the same MedDRA system organ class and preferred term for a particular patient will only be counted once and the denominator for the percentage calculation will be the number of patients in the safety population.

All adverse event summary tables will be presented by dose level (control and 400mg).

- Qualitative sputum microbiology: changes from baseline
- Physical examination: changes from baseline
- Laboratory safety tests: changes from baseline
- Bronchodilator response: before and after treatment

8.3. Justification of Sample Size

8.3.1 Two Arm Study Design

The primary objective of the study is to show an effect of IDPM compared with control on FEV_1 in CF patients.

Sample size was estimated based on the primary and secondary objectives of demonstrating an effect on FEV_1 of IDPM in both patients taking RhDNase and the combined RhDNase and non-RhDNase patient group, and the secondary objective to detect a change in exacerbation rates.

A total of 340 patients will be randomised in a ratio of 3:2 (IDPM 400mg BD: control). It is expected that approximately two thirds of the patients will be taking concurrent RhDNase and approximately 20% of patients will drop out of the trial by the end of the 26 week blinded phase. Therefore there will be approximately 163 evaluable patients in the mannitol arm and 109 evaluable patients in the control arm of the trial. Of these evaluable patients, approximately 109 patients in the mannitol arm and 73 patients in the control arm will be taking concurrent RhDNase.

With 109 patients in the IDPM arm and 73 patients in the control arm taking concurrent RhDNase, the study will have 80% power to detect a difference of 85mL in change from baseline of FEV_1 between the IDPM and control arms in this subgroup of patients. With 50% more patients in each arm of the study when not restricted to patients currently taking RhDNase, the study will have 80% power to detect a difference of 70mL in change from baseline of FEV_1 between the IDPM and control arms. The study will also have more than 80% power to detect a difference in rates of pulmonary exacerbations over the course of a 26 week study, assuming pulmonary exacerbation rates of 0.42 events per patient-year in patients treated with IDPM, and 0.96 events per patient-year in patients in the control group.

Details and further discussion of the sample size estimation used are shown in Appendix 4.

8.3.2 Interim Analysis and Multiple Statistical Comparisons

An interim analysis is planned for midway through the study and a type I error rate of 5% will be maintained by using the Peta-Haybittle rule. This means a significance level of 0.001 will be used for testing the efficacy endpoint at the interim analysis and a significance level of 0.0498 will be used for testing the primary efficacy endpoint at the end of the study.

No adjustment will be made to the significance level for the multiple statistical comparisons conducted as part of the secondary analyses.

8.4 Study Population

8.4.1 Sample Population

Cystic fibrosis, aged $\geq$ 6 years, baseline FEV_1 $\geq$30% and <90% predicted, either gender, not be pregnant or breast feeding, no intolerance to mannitol or beta agonists, not participating concurrently or within the previous 4 weeks in another investigative drug study. No concurrent use of hypertonic saline or beta blockers.

8.4.2 Intent to Treat Population (ITT)

All subjects who are randomised and commence study medication (IDPM or control).

8.4.3 Per Protocol Population (PP)

The PP population includes all subjects with no major protocol violations that have demonstrated an $\geq$80 % compliance with the intervention.

8.4.4 Safety Population

The safety population are those who are randomised and have been administered IDPM/control on at least one occasion.

8.4.5 Statistical Criteria for Study Termination

The study will be terminated once the required numbers of subjects to meet statistical analysis requirements above have completed the protocol successfully.

8.5 Data Analysis Considerations

Results will be summarized overall using univariate statistics including means, standard deviations, ranges (including missing responses), medians and proportions (including cross tabulations), as appropriate to the data. Where necessary, log normalization will be undertaken to produce geometric means, and for use in subsequent statistical tests. Safety data collected will be analysed using descriptive statistics - means, proportions and confidence intervals, documenting the number, severity and type of adverse events, and changes from baseline to follow up in vital signs. Where appropriate, F tests and χ^2 tests will be performed to determine significant before/after changes, and differences between the study groups. The safety analysis will be performed on the safety population.

The primary and key secondary analyses will use generalised linear models to compare the study groups in regards to FEV_1. Adjustments in the models will be made for age and sex, and

disease severity Treatment group will be included in the model as a categorical variable. Should the overall model fit be significant at the 5% level, orthogonal contrasts will be performed using the baseline (pre-intervention) level as the reference to examine changes over time in the outcome. The models will be analysed using SAS V9.1. The findings will include the slope, standard error, and significance tests of the model and study protocol indicator.

8.5.1 Handling of Dropouts and Missing Data

The primary endpoint will be estimated using ITT and PP populations (results from the ITT analysis will take precedence over findings from the PP analysis). All other measures will be performed using the ITT population and where applicable also the PP population. Where a subject has missing data on a continuous outcome measure, the baseline score will be used. This replacement is appropriate since it is expected that scores will improve from or remain similar to baseline, rarely getting worse.

The pattern of missing data for the primary endpoint variable will be summarised descriptively. If there is evidence of differential distribution of missing data between groups, consideration will be given to conducting a secondary efficacy analysis based on the primary efficacy analysis, using an alternative data imputation method (to be defined in the statistical analysis plan of this study).

8.5.2 Efficacy Analyses and Data Monitoring

As indicated in Section 7.5 the data safety monitoring board will examine accumulated outcome and safety data in order to make recommendations concerning continuation, termination or modification of the trial based on the effects of the interventions under study. As part of this process an interim analysis of the primary endpoint is planned when 170 patients have completed the 26 week blinded phase of the study.

In order to control the overall type I error rate at 5% due the significance level used for the analysis of the primary endpoint at the interim analysis will be set at 0.001 and using the Peta-Haybittle rule the significance level for the final analysis will be set at 0.0498.

A safety and efficacy analysis will be conducted at completion of the initial 26 week study for all subjects. A safety analysis will be conducted following the completion of the open label phase.

9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The monitor(s), auditor(s), and regulatory inspector(s) will be given direct access to source data and documentation (e.g. medical records, laboratory reports, diagnostic imaging etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements and privacy regulations.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Amendments and Protocol Violations

No changes from the final approved (signed) protocol will be initiated without the ethics committee's prior written approval or favourable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration. The Principal Investigator(s) and the Sponsor must sign any protocol amendments.

Any deviation from the protocol when no approved amendment exists will be regarded as a protocol violation, and will be addressed as such during the reporting of the study. Protocol deviations must be approved by Pharmaxis in writing before they occur and one protocol waiver does not indicate that a precedent has been set.

10.2 Information to Study Personnel

The Investigator(s) is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting the practical performance of the study and during the course of the study (e.g. when new staff become involved).

The monitor(s) is responsible for initiating the site, for ensuring site compliance with the protocol and for closing out the site at the end of the study. Additional information available during the study should be given as agreed upon, either by the Investigator(s) or the monitor(s), and always when new staff members become involved in the study.

10.3 Study Monitoring

For this study, the average monitoring frequency is expected to be once every eight to ten weeks, but is subject to recruitment rates. The monitor(s) or Sponsor representative is responsible for ensuring that the study is conducted according to Standard Operating Procedures (SOPs) to ensure compliance with Good Clinical Practice (GCP).

The monitor(s) is the primary link between the Sponsor and the Investigator. The main responsibilities of the monitor(s) are to visit the Investigator before, during, and after the study to ensure adherence to the protocol, and to assure that all data are correctly and completely recorded and reported and that informed consent is obtained and recorded for all subjects before their participation in the study.

The monitor(s) will contact and visit the Investigator at regular intervals throughout the study. The monitor(s) will be allowed to check and verify the various records (eCRFs and other pertinent data records) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of the study progress other Sponsor personnel may, on request, accompany the monitor(s) on visits to the study centre. The Investigator and assisting staff must

agree to cooperate with the monitor(s) to resolve any problems, errors, or possible misunderstandings concerning the data detected in the course of these monitoring visits.

10.4 Audit and Inspection

According to ICH Guidelines on GCP, the Sponsor may audit the investigational site to compare raw data, source data, and associated records with the interim (if applicable) or final report of the study to assure that data have been accurately reported. The Sponsor's Clinical Research Department is responsible for the auditing of the study. Auditing may be contracted to an external body.

The Investigator(s) must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP.

11 ETHICS

11.1 Informed Consent

This study will be conducted in full accordance with the current revision of the Declaration of Helsinki and the *Good Clinical Practice: Consolidated Guideline* approved by the International Conference on Harmonization (ICH).

This study will be conducted in compliance with ICH Guidelines for informed consent. Written informed consent will be obtained from each subject before any procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

The subject's willingness to participate in the study will be documented in writing in a consent form, which will be signed by the subject with the date and time of that signature indicated. The Investigator(s) will keep the original consent forms and copies will be given to the subjects.

Written and/or oral information about the study in a language understandable by the subject will be given to all subjects. The information provided must include an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force.

11.2 Health Authorities and Independent Ethics Committees/Institutional Review Boards

The Investigator(s) will ensure that the conduct of the study conforms to the Declaration of Helsinki (current revision) and with national laws and regulations for clinical research.

Before starting this study, the protocol will be submitted to the national/local health authorities and to the IEC/IRB for evaluation. As required, the study will not start before the IEC/IRB and health authorities give approval or a favourable opinion.

11.3 Confidentiality Regarding Study Subjects

The Investigator(s) must assure that the privacy of the subjects, including their personal identity and all personal medical information, will be maintained at all times. In eCRFs and other documents submitted to the Sponsor, subjects will not be identified by their names, but by an identification code (e.g. subject or screen number).

Personal medical information may be scrutinized for the purpose of verifying data recorded on the eCRF. This may be done by the monitor, properly authorized persons on behalf of the Sponsor's quality assurance unit, or competent authorities. Personal medical information will always be treated as confidential, according to local privacy regulations.

12 DATA HANDLING AND RECORD KEEPING

12.1 Completing, Signing, and Archiving Case Report Forms

The Investigator(s) must keep a separate subject identification list showing code numbers, names, and dates of birth to allow unambiguous identification of each subject included in the study. A note will be made in the hospital or clinical medical records, if appropriate, that the subject is participating in a clinical study.

All eCRF visits should be signed by the study coordinator. Any corrections to the data will be made in a manner that does not obscure the original entry and will be dated and initialled by the Investigator or assigned designee. An audit trail will secure all changes in the data flow over time.

It is important to have data collection in a timely manner, meaning that the Investigator/study coordinator shall complete the eCRF pages continuously and ready for monitoring. The monitor(s) and data manager(s) will request additional data and clarification of data through the eCRF page and the queries should be resolved on an ongoing basis. It is important to have all queries resolved as soon as possible.

The data collection will be performed using an electronic data capture solution. Data should be entered by the site in a timely manner during the subject visit. The monitor(s) and data manager(s) will request additional data and clarification of data through the eCRF page and the queries should be resolved as they arise. When the monitor has completed the source data verification and all queries have been resolved the eCRF page will be locked.

12.2 Data Management and Data Control

The Sponsor will be responsible for the processing and quality control of the data. Data management in connection with electronic data capture technique is quite different with a traditional paper CRF. The data management process is carried out by programming of eCRF pages with respect to measurement intervals and logical checks. The monitor(s) fulfils a portion of the data management function by reviewing the eCRF pages and the verification through the source data verification (SDV) process.

Source data, source documents, completed eCRFs, copies of protocols and protocol amendments, drug accountability forms, correspondence, subject identification lists, informed consent forms, and other essential documents must be retained for a period of at least 15 years or at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the Sponsor to inform the Investigator(s)/institution(s) when these documents need no longer be retained. The original record of the eCRFs, will be archived by the Sponsor for the lifetime of the product. No study document or image should be destroyed without prior written agreement between the Sponsor and the Investigator(s). Should the Investigator(s) wish to assign the study records to another party or move them to another location, advance written notice should be given to the Sponsor.

13 FINANCING AND INSURANCE

A separate financial agreement (Investigator Agreement) will be made between each Principal Investigator/Institution/Authority/Clinical Research Organization and Sponsor before the investigational drug is delivered.

The study is covered under a Pharmaxis Ltd liability insurance policy. The certificate of insurance and an information leaflet containing essential information about the insurance coverage can be provided upon request.

14 REPORTING AND PUBLICATION OF RESULTS

The Sponsor is responsible for preparing a clinical study report, in cooperation with the Investigator(s). The final report is signed by the Sponsor and the Principal/Coordinating Investigator.

Policies regarding the publication of the study results are defined in the Investigator Agreement.

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16 APPENDICES

Appendix 1: Time and Events Schedule

Event	Screening Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Visit due at week	**Day -14**	**0**	**6**	**14**	**26**	**38**	**52**
		26 weeks IDPM/control Blinded phase				**26 weeks Open label phase**	
Informed Consent [1]	X[1]				X[4]		X[7]
Inclusion/exclusion criteria	X						
Medical History /Demographics	X						
Concomitant medications	X	X	X	X	X	X	X
Physical examination/ vital signs	X	X	X	X	X	X	X
Pulmonary function tests [2]	X	X	X	X	X	X	X
FOT**		X	X	X	X		
Bronchodilator response test		X			X		
Pregnancy Test[3]	X				X[4]		X[7]
Cystic Fibrosis Questionnaire		X		X	X		
Pulmonary exacerbations review			X	X	X	X	X
Medical resource use review			X	X	X	X	X
Blood tests	X				X		X
Randomise subject	X						
Administer treatment dose in clinic		X		X	X[4*]		
Phone call to subject					X[6]		
Aridol-MTT procedure	X						
Dispense study medication & beta agonist		X	X	X	X[4]	X	X[7]
Weigh treatment induced sputum sample		X		X			
Sputum qualitative micro	X	X	X	X	X	X	X
Issue study diary / Collect diary		X			X[4] / X[5]		X
Adverse event assessment		X	X	X	X	X	X
Drug compliance and accountability			X	X	X	X	X
Discharge subject from study					X[5]		X[5*]

1. Consent may be obtained before screening visit but MUST be obtained prior to any protocol procedures being performed.
2. Medications that effect spirometry must be withheld prior to pulmonary function tests
3. Women of childbearing potential only
4. Only if continuing in open label phase (*receives first dose of open label IDPM)
5. If not continuing in open label phase

5* If not continuing in the 2nd open label phase

6. 4 weeks into open label phase

** Selected sites only (Papworth, RCH)

7. Only if continuing into the 2nd open label phase

Appendix 1A: Time and Events Schedule for the 2nd Open Label Phase

Event	Visit 7	Visit 8
Visit due at week	**64**	**78**
	26 weeks IDPM	
Concomitant medications	X	X
Physical examination/ vital signs	X	X
Pulmonary function tests (medication withholding periods apply)	X	X
Pulmonary exacerbations review	X	X
Medical resource use review	X	X
Blood tests		X
Dispense study medication & beta agonist	X	
Sputum qualitative micro	X	X
Collect diary		X
Adverse event assessment	X	X
Drug compliance and accountability	X	X
Discharge subject from study		X

Appendix 2: CFQ-R

CFQ –R questionnaire

Understanding the impact of your illness and treatments on your everyday life can help your healthcare team keep track of your health and adjust your treatments. For this reason, this questionnaire was specifically developed for people who have cystic fibrosis. Thank you for your willingness to complete this form.

Instructions: The following questions are about the current state of your health, as you perceive it. This information will allow us to better understand how you feel in your everyday life.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

Please fill-in the information or check the box indicating your answer.

Section I Demographics

A. What is your date of birth?

B. What is your gender? ☐ Male ☐ Female

C. During the **past two weeks**, have you been on vacation or out of school or work for reasons **NOT** related to your health? ☐ Yes ☐ No

D. What is your current marital status?

☐Single/never married ☐Married ☐Widowed ☐Divorced ☐Separated ☐Remarried ☐With a partner

E. Which of the following best describes your racial background?

☐ Caucasian ☐African American ☐ Hispanic

☐ Asian/Oriental or Pacific Islander ☐ Native American or Native Alaskan

☐ Other (please describe)_____☐ Prefer not to answer this question

F. What is the highest grade of school you have completed?

☐ Some high school or less ☐ High school diploma/GED ☐ Vocational school ☐ Some college

☐ College degree ☐Professional or graduate degree

G. Which of the following best describes your current work or school status?

☐ Attending school outside the home ☐ Taking educational courses at home ☐ Seeking work

☐ Working full or part time (either outside the home or at a home-based business) ☐ Full time homemaker

☐ Not attending school or working due to my health ☐ Not working for other reasons

Section II. Quality of Life ***Please check the box indicating your answer.***

*During the past **two weeks**, to what extent have you had difficulty:*	**A lot of difficulty**	**Some difficulty**	**A little difficulty**	**No difficulty**
1. Performing vigorous activities such as running or playing sports	☐	☐	☐	☐
2. Walking as fast as others	☐	☐	☐	☐
3. Carrying or lifting heavy things such as books, groceries, or school bags	☐	☐	☐	☐
4. Climbing one flight of stairs	☐	☐	☐	☐
5. Climbing stairs as fast as others	☐	☐	☐	☐
***During the past two weeks**, indicate how often:*	**Always**	**Often**	**Sometimes**	**Never**
6. You felt well	☐	☐	☐	☐
7. You felt worried	☐	☐	☐	☐
8. You felt useless	☐	☐	☐	☐
9. You felt tired	☐	☐	☐	☐
10. You felt energetic	☐	☐	☐	☐
11. You felt exhausted	☐	☐	☐	☐
12. You felt sad	☐	☐	☐	☐

Please circle the number indicating your answer. Please choose only one answer for each question.

*Thinking about the state of your health over the last **two weeks**:*

13. To what extent do you have difficulty walking?
You can walk a long time without getting tired
You can walk a long time but you get tired
You cannot walk a long time because you get tired quickly
You avoid walking whenever possible because it's too tiring for you

14. How do you feel about eating?
Just thinking about food makes you feel sick
You never enjoy eating
You are sometimes able to enjoy eating
You are always able to enjoy eating

15. To what extent do your treatments make your daily life more difficult?
Not at all
A little
Moderately
A lot

16. How much time do you currently spend each day on your treatments?
A lot
Some
A little
Not very much

17. How difficult is it for you to do your treatments (including medications) each day?
Not at all
A little
Moderately
Very

18. How do you think your health is now?
Excellent
Good
Fair
Poor

Please select a box indicating your answer.

*Thinking about your health during the past **two weeks**, indicate the extent to which each sentence is true or false for you.*

	Very True	**Somewhat true**	**Somewhat false**	**Very false**
19. I have trouble recovering after physical effort	☐	☐	☐	☐
20. I have to limit vigorous activities such as running or playing sports	☐	☐	☐	☐
21. I have to force myself to eat	☐	☐	☐	☐
22. I have to stay at home more than I want to	☐	☐	☐	☐
23. I feel comfortable discussing my illness with others	☐	☐	☐	☐
24. I think I am too thin	☐	☐	☐	☐
25. I think I look different from others my age	☐	☐	☐	☐
26. I feel bad about my physical appearance	☐	☐	☐	☐
27. People are afraid that I may be contagious	☐	☐	☐	☐
28. I get together with my friends a lot	☐	☐	☐	☐
29. I think my coughing bothers others	☐	☐	☐	☐
30. I feel comfortable going out at night	☐	☐	☐	☐
31. I often feel lonely	☐	☐	☐	☐
32. I feel healthy	☐	☐	☐	☐
33. It is difficult to make plans for the future (for example, going to college, getting married, advancing in a job, etc.)	☐	☐	☐	☐
34. I lead a normal life	☐	☐	☐	☐

Section III. School, Work, or Daily Activities

Questions 35 through 38 are about school, work, or other daily tasks.

35. ***To what extent did you have trouble keeping up with your schoolwork, professional work, or other daily activities during the past*** *two weeks****?***

You have had no trouble keeping up
You have managed to keep up but it's been difficult
You have been behind
You have not been able to do these activities at all

36. How often were you absent from school, work, or unable to complete daily activities during the last two weeks because of your illness or treatments?

☐ Always ☐ Often ☐ Sometimes ☐ Never

37. How often does CF get in the way of meeting your school, work, or personal goals

☐ Always ☐ Often ☐ Sometimes ☐ Never

38. How often does CF interfere with getting out of the house to run errands such as shopping or going to the bank?

☐ Always ☐ Often ☐ Sometimes ☐ Never

Section IV. Symptoms Difficulties

Please select a box indicating your answer.

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

	A great deal	**Somewhat**	**A little**	**Not at all**
39. Have you had trouble gaining weight?	☐	☐	☐	☐
40. Have you been congested?.....	☐	☐	☐	☐
41. Have you been coughing during the day?.....	☐	☐	☐	☐
42. Have you had to cough up mucus?	☐	☐	☐	☐ **Go to Question 44**

43. Has your mucus been mostly: ☐ Clear ☐ Clear to yellow ☐ Yellowish-green ☐ Green with traces of blood ☐ Don't know

How often during the past ***two weeks:***	**Always**	**Often**	**Sometimes**	**Never**
44. Have you been wheezing?.....	☐	☐	☐	☐
45. Have you had trouble breathing?	☐	☐	☐	☐
46. Have you woken up during the night because you were coughing?.....	☐	☐	☐	☐
47. Have you had problems with gas?	☐	☐	☐	☐
48. Have you had diarrhoea?.....	☐	☐	☐	☐
49. Have you had abdominal pain?.....	☐	☐	☐	☐
50. Have you had eating problems?	☐	☐	☐	☐

Please be sure you have answered all the questions.

THANK YOU FOR YOUR COOPERATION!

Appendix 3: Study Diary (English)

IDPM Study Diary

Name:…….

Study Doctor:_____ Ph _____ Coordinator:_____ Ph_____

Appointments:

Base Study Visits

Visit 1 _____ (study medication taken under supervision in clinic)

Visit 2_____

Visit 3 _____ (study medication taken under supervision in clinic)

Visit 4 _____ (study medication taken under supervision in clinic if continuing in open label phase)

1st Stage Open Label Visits

Visit 5 _____

Visit 6 _____

2nd Stage Open Label Visits

Visit 7_____

Visit 8 _____

If you are unsure about any requirements in this study, please telephone your study coordinator at the phone number above.

Please review this diary each day

At each visit: Study medication should not be taken within 12 hours of your visit. bring with you:

- **your study medication – empty and unused blisters**
- **your study diary**

- **withhold medications as listed on page 3 of this diary**

Smoking, alcohol, heavy meals and strenuous exercise should be avoided on clinic visit days until all procedures have been completed.

Table of Contents

MEDICATION WITHHOLDING PERIODS BEFORE YOUR CLINIC VISIT

- The medications listed below must be withheld prior to all clinic visits as they may effect your lung function tests (spirometry). If you forget to withhold your medications you should notify your study co-ordinator to reschedule your appointment.

Medications That May Influence Spirometry Results

Medication	Minimum time interval from last dose until spirometry
IDPM or control (study medication)	12 hours
Short acting reliever medications *eg salbutamol (Ventolin, Respolin, Airomir, Asmol, Epaq, Resmax, Combivent); terbutaline (Bricanyl)*	6 hours
Long acting reliever medications *eg salmeterol (Serevent); eformoterol (Oxis, Foradil)*	12 hours
Combination drugs *e.g. Fluticasone and salmeterol (Seretide, Advair), budesonide and eformoterol (Symbicort)*	12 hours

ORDER OF DAILY PROCEDURES

The recommended order of treatment procedures is:

1. bronchodilator
2. IDPM/control
3. physiotherapy / exercise
4. RhDNase
5. inhaled antibiotics
6. inhaled cortico-steroids

Only if applicable

Adverse events *Record any health problems that are unusual for you. We would like to know what the problem is, when it started and how long it lasted for. If you took any medicine to treat it, we would like to know this as well.*

Health Problem	Date / time started	Date / time finished	How did you treat the problem	Was the problem mild, moderate or severe? (see below *)
Eg: toothache	*23 Mar 05*	*26 Mar 05*	*Pain relief*	*moderate*

** Mild - awareness of sign or symptom but easily tolerated*
Moderate - discomfort causes interference with usual activity
Severe - incapacitating, or unable to do usual activities

Medicines: *If you take any new medicines or change the amount of medicine you are already taking please record it below. We would like to know when you started taking this medicine, when you stopped, how much you took and why you took it. Do not include IDPM/control.*

Medicine	Date started	Date finished	How much did you take?	Why did you take it?
Eg Aspirin	23 March 05	26 March 05	2 x 300mg twice a day	toothache

Community Visits *(do not include hospital visits)*

Doctors, Nurses, Physiotherapists Visits

If you visit the doctor, nurse or physiotherapist for any reason, we would like to know when, where and why you went.

Who did you visit? 1. Hospital doctor (specialist) 2. GP 3. Nurse 4. Physiotherapist 5. Other health care professional (specify)	**Type of contact?** 1. Home visit 2. GP 's surgery 3. Phone call 4. other (specify)	**Date of visit**	**Why did you have this visit?**	**Did you have any procedures done?** Chest Xray, blood draw, ultrasound, injection, etc
2. GP	2. GP's surgery	26th May 2004	Chest infection	Chest Xray

Hospital Visits: *If you go to the hospital for any reason we would like to know about it. This includes visits when you are admitted to hospital or attend as an outpatient, or as a day only admission.*

Type of hospital visit	Date (s)	Reason	Procedures	Hospital	Doctor
Admission *(overnight stay of 1 night or more)*	1st June 2006 – 5th June 2006	Abdominal Pain	Abdo ultrasound Abdominal X-ray IV fluids Appendicectomy	St Elsewhere	Dr Who
Day case *(admitted but discharged same day)*	6th July 2006	Wisdom tooth extraction	IV antibiotics IV sedation	St Beenthere	Dr What
Outpatient *(seen in clinic or emergency dept)*	31st August 2006	CF check-up	Lung function tests	St Notgonthere	Dr When

Pharmacists Visits: *If you visit the pharmacist to have a prescription filled or buy any over the counter medicines, we would like to know about them.*

Medicine	Date	How much did you buy?
Amoxicillin Capsules	*17th August 2006*	*1 pack of 500mg*

Appendix 4 Sample Size Assumptions and Calculations

A total sample size of 340 patients is planned for the CF-301 study and random allocation will be based on having 3 patients in the IDPM 400mg BD arm for each 2 patients in the control arm therefore approximately 204 patients will be randomised to receive IDPM 400mg BD and 136 will be randomised to receive control therapy. It is expected that two-thirds of patients will be taking concurrent RhDNase so approximately 136 of the patients in the IDPM arm and 90 patients in the control arm will be taking concurrent RhDNase.

Assuming a drop out rate of 20% over the 26 week study period, 163 patients in the IDPM arm (109 taking RhDNase and 54 not taking RhDNase) and 109 patients in the control arm (73 taking RhDNase and 36 not taking RhDNase) will complete the study.

The primary hypothesis, that there is no difference in change from baseline FEV1 (ΔFEV_1) between patients taking concurrent RhDNase in the IDPM group and patients taking RhDNase in the control group, will be tested using a repeated measures technique implemented using a generalised linear mixed model. Age, disease severity at baseline, and baseline FEV1 will be included in the model as covariates. However, the sample size calculation is based on the sample size required for an analysis using an independent two sample t-test, which would be expected to underestimate the power of the repeated measures analysis and therefore can be considered conservative. Based on this sample size the study would have 80% power to detect a difference in change between groups of 70m/L at the 4.98% significance level. In the CF-201 phase II study a difference in change in FEV of 120m/L was observed between treatment groups but the standard error of the estimate was 33m/L indicating the lower confidence limit of a treatment benefit is approximately 50m/L, which is still a clinical significance improvement and therefore we believe the detectable difference in this study is appropriate.

The sample size calculation is based on the following criteria and assumptions:

- Significance level (α) = 0.0498
- Power ($1-\beta$) = 0.80
- Standard deviation (SD) of the outcome of interest (ΔFEV_1) = 200m/L

The rational for using $\alpha = 0.0498$ is to control the overall type I error rate at 5% due to analysing the primary efficacy endpoint during the interim analysis. The analysis of the primary endpoint at the interim analysis will be based on $\alpha = 0.001$ and therefore using the Peto-Haybittle rule the significance level for the final analysis should be set at 0.0498. The estimate of the SD is based on the results of the CF-201 phase II study.

When the analysis is restricted to patients who are currently treated with RhDNase (approximately 109 vs 73 patients) the study will have 80% power to detect a difference in change in FEV of 85m/L at the 5% significance level.

The above sample size calculations were performed using the PS software package and verified by an independent statistician using Proc Power in SAS.

Pulmonary Exacerbations

Pulmonary exacerbation rates represent a secondary endpoint of interest. The definition of exacerbation varies between studies, and so it is difficult to find consistent estimators of the number of events and the time to first event/symptom. The assumptions made in this section are based upon a study of hypertonic saline in patients with cystic fibrosis [32]. Amongst 83 patients taking 'active' therapy, an average of 0.39 exacerbations (requiring IV antibiotic therapy) per patient were observed, whilst among 81 patients taking 'control' therapy, 0.89 exacerbations per patient were observed. Assuming full patient follow-up in this 48 week study, this corresponds to rates of 0.42 events per patient-year in the 'active' group and 0.96 events per patient-year in the 'control' group. The rate ratio is 0.42/0.96=0.44.

The rate of exacerbation events per patient-year are assumed to be distributed as independent Poisson processes. Calculation of the sample size required to detect this difference in rates is formulated as follows:

$$N = ((1/\lambda_1 + 1/\lambda_2) \times (Z_\alpha+Z_\beta)^2) / (\ln\lambda_1 - \ln\lambda_2)^2$$

where λ_i is estimated event rate in group i. The values Z_α and Z_β represent values of the standard normal distribution that correspond to a type I error rate of α=0.025 and a type II error rate of β=0.2 (corresponding to statistical power of 80%), respectively. Using estimates of λ_1 = 0.42, λ_2 = 0.96, and directly computed values of Z_α=1.960 and Z_β=0.842, with 79 patients, each followed for 26 weeks, there is 80% power to detect the difference in exacerbation rates.

Appendix 5 Protocol versioning history

Version & Date	Description
Version 1 – 08 August 2006	Original (not submitted)
Version 2 – 22 December 2006	Amendment 1
Version 3 – 12 March 2007	Amendment 1 & Addendum
Version 3 (UK) – 12 March 2007	Amendment 1 & Addendum
Version 4 – 16 August 2007	Amendment 2
Version 5 – 16 November 2008	Amendment 3
Version 5.1 – 23 July 2009	Administrative change 1

17 SIGNATURE PAGES

Protocol DPM-CF-301

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principals stated in the latest version of the Declaration of Helsinki. I agree to report all information or data in accordance with the protocol, and in particular, I agree to report any serious adverse events. I will accept the monitors', auditors', and regulatory inspectors' oversight of the study. I will abide by the publication plan set forth in the investigator agreement with Pharmaxis. I will promptly submit the protocol to the applicable ethical review board.

PRINTED NAME(s)	**SIGNATURE**	**DATE**
_____	_____	_____
Principle Investigator		
_____	_____	_____
Sponsor Representative		

Clinical Study Protocol DPM-CF-302

Version 2, 4th April, 2008

Long Term Administration of Inhaled Mannitol In Cystic Fibrosis – A Safety and Efficacy Study

§

Sponsor

pharmaxis

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Confidentiality Statement

SYNOPSIS

Title*:* Long Term Administration of Inhaled Mannitol in Cystic Fibrosis – A Safety and Efficacy Study

Sponsor: Pharmaxis Limited, 2/10 Rodborough Road, Frenchs Forest, NSW 2086 Australia.

Primary objective

- To determine whether inhaled mannitol compared to control improves FEV_1 in patients with CF

Secondary Objectives

- To determine whether inhaled mannitol compared to control improves FEV_1 in patients with CF on existing RhDNase treatment
- To assess whether inhaled mannitol treatment:
  * Reduces pulmonary exacerbations in those taking RhDNase as a sub-group and in the total cohort
  * Improves quality of life
  * Reduces days on IV antibiotics, rescue oral or inhaled antibiotics
  * Reduces days in hospital due to pulmonary exacerbations
  * Improves other measures of lung function
  * Demonstrates an appropriate safety profile (adverse events, hematology, biochemistry, sputum microbiology, physical examination)
  * Reduces hospital and community care costs

No. of Subjects: Minimum 300 subjects to be randomized

Period of enrolment*:* 12 months

Number of subject visits: 7

Duration of study treatment: 26 weeks blinded followed by 26 weeks open label

Study design: Randomized, controlled, parallel arm, double blind proceeding to open label

Study population: Cystic fibrosis, aged $\geq$6 years, baseline FEV_1 $\geq$40% and <90% predicted, not pregnant or breast feeding, no intolerance to mannitol or $ß_2$agonists, no concurrent use of hypertonic saline or ß blockers for the study duration.

Name of study drug*:* Dry powder mannitol for inhalation

Dose and administration rate: 400 mg BID or control

Blinding: Double-blind

Indication: Cystic Fibrosis

Drug Administration*:* Inhalation via dry powder inhaler (Osmohaler HR)

Primary Endpoint: Change in absolute FEV_1

Secondary Endpoints:

Efficacy:

- Change in absolute FEV_1(rhDNase group)
- Pulmonary exacerbations in those taking rhDNase as a sub-group and in the total cohort
- Quality of life scores using Cystic Fibrosis Questionnaire-R
- Rescue antibiotic use (number of agents, course and days of use)
- Change in absolute FVC, FEF_{25-75} from baseline
- Days in hospital due to pulmonary exacerbations

Safety:

- Adverse events
- Laboratory safety tests: complete blood count, blood urea nitrogen, electrolytes, liver function tests
- Qualitative sputum microbiology
- Quantitative sputum microbiology for S. *aureus* and P. *aeruginosa*
- Physical examination findings

Cost-Effectiveness:

- Total costs incurred in intervention and control groups
  * Costs associated with inhaled mannitol
  * Cost of antibiotic use and rescue medication
  * Costs of hospitalizations and other secondary care services used
  * Cost of primary and community care services used
- Indicators of effectiveness and quality of life for intervention and control groups
  * As above
- Determination of cost-effectiveness ratios
- Sensitivity analysis
  * To assess extent to which variation in parameter estimates affect cost effectiveness ratios

TABLE OF CONTENTS

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LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AHR	Airway Hyperresponsiveness
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
BID	Twice a day
BHR	Bronchial hyperresponsiveness
BMC	Bronchial mucus clearance
BP	Blood Pressure
BP	British pharmacopoeia
BTPS	Body Temperature Pressure Saturation
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CFTR	Cystic fibrosis transmembrane regulator
cGMP	Current Good Manufacturing Practice
CPK	Creatine Phosphokinase
CRF	Case Report Form
CRO	Clinical Research Organization
DCF	Data Clarification Form
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DSMB	Data safety monitoring board
DPI	Dry powder inhaler
ECG	Electrocardiogram
ESS	Epworth sleepiness scale
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEF_{25-75}	Measure of Small Airway Limitation
FEV_1	Forced Expiratory Volume in 1 Second
FEV_1/FVC	Index of Airflow Limitation
FOT	Forced oscillation technique
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transpeptidase
GLP	Good Laboratory Practice
HR	Heart rate
HRCT	High Resolution Computed Tomography Scan
HRQOL	Health related quality of life
HS	Hypertonic saline
HUI	Health utilities index
IB	Investigators brochure
ICH	International Conference on Harmonization
ICS	Inhaled cortico steroids
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IMP	Investigational Medicinal Product
ITT	Intent-to-treat
LABA	Long acting bronchodilator

LDH	Lactate Dehydrogenase
LCQ	Leicester Cough Questionnaire
LFT	Liver function tests
MCC	Mucociliary clearance
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Cell Volume
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MRSA	Methicillin Resistant Staph Aureus
MSLI	Multiple Stage Liquid Impinger
MTT	Mannitol tolerance test
0_2	Oxygen
Osmohaler HR	High resistance inhaler device
PD20	Provocative Dose causing a 20% fall in FEV1
PC20	Provocative Concentration causing a 20% fall in FEV1
PEF	Peak Expiratory Flow
PEG	Percutaneous gastrostomy
PP	Per Protocol
PRN	As Required
QoL	Quality of Life
QALY	Quality adjusted life years
RR	Respiratory rate
RTI	Respiratory tract infection
SABA	Short acting bronchodilator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGRQ	St George's Respiratory Questionnaire
SpO2	Oxygen Saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	Therapeutic Goods Administration
USP-NF	Unites States Pharmacopeia – National Formulary
UNITS OF MEASURE	
cm	Centimeter
^{o}C	Degrees Celsius
^{o}F	Degrees Fahrenheit
hr	Hour
ht	Height
kg	Kilogram
L	Liter
L/min	Liters per minute
Lb	Pounds
Mcg	Micrograms
MEq/L	Mill equivalents per liter
Mg	Milligrams
Min	Minutes
mL	Milliliter
mOsmol	Milliosmol
sec	Second
µm	Micrometer
w	Watts
wt	Weight

1 INTRODUCTION AND BACKGROUND INFORMATION

Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder of exocrine glands with a heterozygote frequency of 1 in 20 to 1 in 25 individuals. It is the most common lethal genetic disorder affecting Caucasian populations and in spite of genetic counseling, the number of patients with CF is likely to continue to increase for some time as the median survival increases. Prognosis for those with the disease has significantly improved over the past fifty years[1] with the median survival age in the United States being 36.5 years in 2005[2].

An understanding of the pathophysiological mechanisms underlying the lung disease in CF is still to be clarified[3-6]. It is thought that the failure of the cystic fibrosis transmembrane regulator (CFTR) results in hyperabsorption of Na+ ions and resorption of fluid from the mucosal to the luminal surface of the lung epithelium. This causes a dehydration of airway secretions with consequent impaction of mucus plaques on cilia and failure of mucus transport up through the bronchi. The lung in CF is characterized by accumulation of thick mucus, chronic bacterial infections and chronic obstructive lung disease. Much of the morbidity and mortality is due to respiratory disease, related to the presence of tenacious sputum, and chronic infection and inflammation. Whether inflammation precedes infection or is an exaggerated consequence of infection is unknown. However by mid childhood, most patients have increased airway secretions, and enhancing mucus clearance with physical techniques (for example active cycle of breathing, positive pressure, and autogenic drainage) is a major goal of therapy.

The mechanism whereby inhaled mannitol increases mucociliary clearance of mucus remains unclear. A combination of factors, which include changes in the rheology of mucus favoring ciliary and cough clearance may be responsible[7-10]. Osmotic agents may change the viscoelastic properties of the mucus by reducing the number of entanglements that mucin polymers form. While ionic agents may achieve this by shielding the fixed charges along the mucin macromolecules, the non-ionic agents may achieve this by disrupting the hydrogen bonds between mucins[9,10]. Osmotic agents also have the potential to increase the amount of water in the airway lumen. Thus, increased hydration may also contribute to an increase in the transportability of mucus. Additionally, osmotic agents may increase clearance of mucus by stimulating mucus secretion. The effect of osmolarity on mucus secretion could be direct or indirect via release of mediators from epithelial and mast cells and neuropeptides from sensory nerves which are known to be secretagogues. Although an increase in mucus secretion is not seen to be a desirable effect, this stimulation of mucus secretion may help increase clearance of viscous and stagnated mucus. Mannitol may benefit patients by reducing the mucus load acutely, or it may have a prolonged effect on mucociliary clearance. Also, as excessive mucus in the airways may result in some limitation of airflow, a reduction in the mucus load may also improve airway function especially in the small airways.

Infected sputum from patients with CF contains high concentrations of DNA from degenerating neutrophils. Since purified DNA solutions are known to have high levels of viscoelasticity, the use of RhDNase has been instituted in CF patients and it has been shown to increase FEV_1 and reduce lung infections in one third to one half of CF patients[11,12]. RhDNase must be considered the "gold standard' mucus clearance agent. However 30-50% of patients do not derive benefit from this treatment. It has previously been shown that hypertonic saline (HS) may also improve bronchial mucus clearance (BMC) in CF patients[13], although not all studies do report an improvement in lung function[10]. Inadequate saline induced osmolarity changes due to the dose and use of a jet nebulizer for delivery may account for the lack of HS effect reported[10]. Of note, two weeks of treatment with either hypertonic saline (HS) or

RhDNase results in a significant improvement in FEV_1 in subjects with CF[13,14]. One likely mechanism by which the HS works is the creation of an osmotic gradient across the airway epithelium with the consequent movement of water into the airway lumen. This would then improve the biorheology of the secretions and the depth of the periciliary fluid layer leading to the enhanced mucus clearance[15]. It has been shown that HS may improve lung function in some RhDNase failures, but there still remains a hard core who respond to neither treatment[16]. Both RhDNase and HS have to be given using a nebulizer, which is time consuming, inconvenient and unpopular. In addition, RhDNase is limited by its high cost and the requirement for refrigeration. It may be advantageous to have an alternative, non-ionic, dry powder osmotic agent for use in CF.

Inhaled mannitol is being developed as a therapeutic agent for the treatment of cystic fibrosis and other diseases characterized by difficult to clear, thickened respiratory mucus. The mucoactive effects of inhaled mannitol have been examined in several acute and short term studies and now warrant further investigation. As part of the development plan, information on the efficacy and safety of inhaled mannitol over the long term is required. Running concurrently is a 6 -12 month sister study, being conducted in the United Kingdom, Ireland, Germany, New Zealand and Australia. Expected to complete in 2009, this study is will further provide efficacy and safety evidence for use in cystic fibrosis.

1.1 Name and Description of Investigational Product

Mannitol ($C_6H_{14}O_6$ MW 182) is a well known, naturally occurring sugar alcohol found in most vegetables and is commonly used as an excipient in the formulation of pharmaceutical products and as a food additive. As an osmotic agent it may be used to induce diarrhea, diuresis and treat cerebral edema. It is a stable substance which as a powder has good flow ability and, because it resists moisture absorption at relative high humidity it is a suitable substance to encapsulate for inhalation.

Mannitol dry powder for inhalation is prepared by spray drying Mannitol BP. No other component/excipient other than water enters the formulation to produce the mannitol solution. The solution is converted to a fine mist through a process of liquid atomization followed by rapid hot air drying. The result is a dry powder of with particles of respirable size and spherical in shape. cGMP product is produced at the Pharmaxis manufacturing facility in Frenchs Forest, Sydney, Australia.

Particle size distribution is tightly controlled and measured by laser diffraction during production. The performance of the product in an inhaler device is then measured in the laboratory using a multiple stage liquid impinger (MSLI) (Astra, Lund, Sweden), or similar device, to calculate aerodynamic particle size distribution.

Further information on the investigational product is given in the Investigator's Brochure.

1.2 Findings from Clinical Studies

Mannitol as a Bronchial Provocation Test

Mannitol as a diagnostic test for airway hyperresponsiveness has received marketing approval in Australia (2006) and Europe (2006-2007). As at April 2007, over four thousand five hundred subjects had been administered dry powder mannitol to test for airway responsiveness commercially and in clinical trials, patients with clinically recognized asthma, and healthy non-asthmatic subjects including 1047 subjects in two major phase 3 studies sponsored by Pharmaxis. Two hundred and thirty six subjects included in the phase 3 studies were below 18 years. Details of the studies that have been fully reported to date can be found in the Investigator's Brochure section 4.

Mucociliary Clearance Studies in Cystic Fibrosis, Bronchiectasis and Asthma

A medical imaging study[17] showed that inhalation of mannitol increased MCC in healthy and asthmatic subjects. The total clearance of radioactivity at 45 minutes post intervention was significantly higher

after mannitol treatment for both the asthmatic and normal subjects. For the asthmatic subjects, the mean total clearances were 55% and 34% for mannitol and control, respectively ($p < 0.002$), and for normal subjects, the values were 41% and 25% for mannitol and control, respectively ($p < 0.002$).

Since β_2-agonists and osmotic agents such as mannitol stimulate mucociliary clearance by different mechanisms that could potentially interact, a study examining the effects of inhaling terbutaline in combination with mannitol was conducted[18]. Healthy and asthmatic subjects received terbutaline or control at set times before and after mannitol. Clearance was measured with a gamma camera. The mannitol-induced increase in mucociliary clearance was transiently inhibited by terbutaline pre-treatment, and transiently enhanced when terbutaline was administered after mannitol. Total clearance of terbutaline plus mannitol was independent of the order of administration. It was concluded that although the timing of administration of terbutaline may transiently affect the rate of clearance produced by mannitol, the overall clearance was not changed.

A pilot scintigraphy MCC study was conducted in12 subjects with CF[13]. Each patient received four treatments: 300 mg mannitol, empty capsules plus coughing, hypertonic saline, and physiological saline plus coughing. Total clearance at 90 minutes was significantly higher for both mannitol and hypertonic saline compared to their respective control treatments. The mean clearance was 28% and 19% for the mannitol and empty capsule plus coughing, respectively ($p < 0.01$), while the mean clearance was 31% and 21% for hypertonic saline and physiological saline plus coughing, respectively ($p < 0.01$).

When given to patients with non-CF bronchiectasis a single dose of 330mg mannitol improved MCC at 75 minutes with a carryover effect still present at 24 hours[19].

Therapeutic Studies in Bronchiectasis

The first in this group of studies was an open label study that examined the effect of 400 mg of mannitol given once daily for 12 consecutive days in 9 subjects with long-term but stable bronchiectasis[8]. This study showed that mannitol improved the quality of life as assessed by the St. George's Respiratory Questionnaire (SGRQ) in particular ease of mucus clearance after mannitol. Of note was the important finding that mannitol did not change the underlying bacterial colonization in these patients.

The administration of 400 mg of mannitol BID for 2 weeks was studied in 60 subjects with non-CF bronchiectasis in two randomized, blinded, crossover studies[20]. The primary objective was to compare the effects of twice daily treatment of mannitol on the disability and handicap associated with bronchiectasis before and after treatment. Disability and handicap was assessed by quality of life (SGRQ), Epworth sleepiness score, symptom questionnaires and exercise testing. Secondary endpoints included sputum microbiology and lung function changes assessed by spirometry and flow oscillometry (FOT).

A statistically significant improvement in the quality of life score (SGRQ, Impact score, $p<0.05$) was observed in patients who complained of an unclear chest at study entry. Statistically significant improvements were also seen overall in daytime sleepiness ($p<0.05$), and in total symptoms score ($p<0.05$). No worsening in bacterial colonization occurred and the adverse events profile was similar and unremarkable across both treatment arms. Small but significant changes in the low-frequency reactance measured by impulse oscillometry were suggestive of improvements in the small airways as a result of mucus clearance[21].

A recently completed phase III study examined the effect of 320mg mannitol BID for 3 months in 362 subjects with bronchiectasis. Data are still being analyzed; however, the results indicate a statistically significant difference in quality of life and 24 hour sputum volume compared to placebo. Quantitative sputum microbiology analysis showed no differences between mannitol and placebo in the number of organisms per gram for H *influenzae*, S. *pneumoniae*, and P *aeruginosa*. In addition, adverse event profiles were similar across both arms.

Therapeutic Studies in Cystic Fibrosis

A phase II randomized, controlled, crossover clinical trial investigated the effect of 2 weeks treatment with mannitol in 39 subjects with cystic fibrosis[22]. While taking mannitol, subjects experienced a 7 % improvement in FEV_1 from baseline ($p<0.001$) with an absolute increase of 121mL. In addition FEF_{25-75} increased by 15.5 % on mannitol ($p<0.01$). FVC increased by 4.6% ($p<0.05$), but was not statistically significant compared with control ($p=0.1$). An improvement in FEF_{25-75} with only small changes in FVC, which is important for the validity of the comparison, suggests that in the small airways the improvement is physiological rather than mechanical. In addition, lung function improved irrespective of disease severity and concomitant rhDNase treatment, suggesting that mannitol has an additive effect to rhDNase.

In the same study, mannitol led to a significant improvement in the respiratory domain of the Cystic Fibrosis Questionnaire (CFQ) and in the respiratory symptom score. Both are suggestive of both lung function improvement, changes in sputum production and a reduction in cough. In addition, chest sounds were improved on mannitol compared with control ($p<0.05$), concordant with respiratory symptom changes. Adverse event profiles were comparable across both mannitol and placebo treatment arms and qualitative sputum microbiology was unchanged in either arm.

Details of these and the pre-clinical studies can be found in the Investigator's Brochure.

1.3 Known and Potential Risks (and Benefits) to Human Subjects

Mannitol currently has a number of medical applications. It is used because it is inexpensive, has no known toxicity and has an excellent safety profile[23]. Mannitol is principally used to raise the osmolarity resulting in enhanced flow of water from tissues while remaining in the extracellular compartment. Mannitol is given orally in doses of up to 200g to induce diarrhea for bowel preparation prior to colonoscopy or surgery[24], and intravenously in a dose of 50 to 200g over a 12 hour period to induce diuresis or up to 0.25g/kg (i.e. approximately 16g for a 65kg subject) over 30 to 60 minutes to treat cerebral edema[25]. In pharmaceutical preparations its primary use is as an excipient in tablets and capsules.

Mannitol is used as a sweetener in the manufacture of foods because of its pleasant taste, low caloric content and rapid elimination from the body. Because it is more slowly fermented by oral micro-organisms than glucose, it decreases the acidification and plaque formation on teeth. While an intake of 10 - 20g will produce a laxative effect, the small quantities used in this study (400mg) are not expected to have laxative effects, nor be detrimental for diabetics.

Inhaled mannitol is known to induce bronchoconstriction in subjects with airway hyperresponsiveness[26]. Hyperresponsive airways have an abundance of mast cells and eosinophils that react to the osmotic stimulus of mannitol by releasing mediators that cause smooth muscle contraction and narrow the airways[27]. This is a typical response in asthmatic subjects with sub-optimal control. Asthmatic subjects who are well controlled on inhaled cortico-steroids, and similarly, non-asthmatics, do not develop bronchoconstriction in response to mannitol[28]. The known bronchoconstrictive response can be successfully blocked by the administration of a bronchodilator prior to mannitol inhalation[29].

Cough tends to occur on inhalation, and appears to be related to inspiratory effort, device resistance and possibly the presence of underlying asthma. In the majority of subjects, mannitol induced cough is short-lived and rarely bothersome; moreover it is an essential and beneficial mechanism to aid mucus clearance.

Nausea and vomiting and sore, dry throat have been reported in small numbers of subjects in past short term studies[30]. Therefore it is recommended that subjects drink water following inhaled mannitol

treatment to rinse the oral cavity and esophagus after inhalation. A single case of hemoptysis requiring hospitalization that was possibly related to mannitol administration has been recently reported.

Mannitol has shown promise in several studies and in this long term study, may benefit patients with cystic fibrosis by facilitating the clearance of stagnant mucus. In doing so improvements in lung function and quality of life; reduction in cough, infective episodes and antibiotic use may result. It is hypothesized that these improvements may be translated to a reduction in associated heath care costs. Mannitol has a pleasant taste, is quick and easy to administer, is highly portable and convenient, and possesses none of the infection control issues or requirement for electricity associated with wet aerosols. It is this potential and the paucity of known adverse effects that support a longer term investigation of its use in cystic fibrosis patients.

1.4 Selection of Drugs and Doses

The dose of inhaled mannitol to be administered in this study, 400mg, has been selected as it within the range (300 - 420mg) previously shown to promote mucus clearance from the lungs in cystic fibrosis and bronchiectasis. An open label two week dosing study currently ongoing, shows a significant increase in FEV_1 at 400 mg BID compared with a sub-therapeutic dose given BID, whereas there is no significant difference between 200 mg BID and control. While the study is yet to complete, there is substantial evidence for a 400mg twice daily dose.

1.5 Compliance Statement

The investigator(s) is responsible for performing the study in accordance with this protocol and the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP), and for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this study in accordance with the protocol will be documented in study agreements with the sponsor, and other forms as required by national authorities in the country where the study centre is located.

The investigator(s) is responsible for ensuring the privacy, health, and welfare of the subjects during and after the study, and must ensure that fully functional resuscitation equipment and personnel trained in its proper use are immediately available in case of a medical emergency. The investigator(s) must be familiar with the background and requirements of the study and with the properties of the study drug as described in the Investigator's Brochure.

The principal investigator at each centre has the overall responsibility for the conduct and administration of the study at that centre, and for contacts with study centre management, the Institutional Review Board (IRB), and with local authorities.

1.6 Population Studied

Male and female subjects with cystic fibrosis, aged $\geq$6 years, baseline FEV_1 $\geq$40% - 90% predicted, not be pregnant or breast feeding, no intolerance to mannitol or beta agonists, no concurrent use of hypertonic saline or beta blockers for the study duration.

Patients will be recruited irrespective of concomitant RhDNase use. The study will recruit enough 'RhDNase using' subjects so that there will be sufficient power to detect changes in this subgroup as well as the total population.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Study Objectives

2.1.1 Primary Objective:

- To determine whether inhaled mannitol compared to control improves FEV_1 in patients with CF

2.1.2 Secondary Objectives:

- To determine whether inhaled mannitol compared to control improves FEV_1 in patients with CF on existing RhDNase treatment

To assess whether inhaled mannitol treatment:

- Reduces pulmonary exacerbations in those taking RhDNase as a sub-group and in the total cohort
- Improves quality of life
- Reduces days on IV antibiotics, rescue oral or inhaled antibiotics
- Reduces days in hospital due to pulmonary exacerbations
- Improves other measures of lung function
- Demonstrates an appropriate safety profile (adverse events, hematology, biochemistry, sputum microbiology, physical examination)
- Reduces hospital and community care costs

2.2 Purpose of Study and Rationale

The purpose of this study is to examine the efficacy and safety of 26 weeks treatment with inhaled mannitol in subjects with cystic fibrosis. Previous studies with inhaled mannitol have demonstrated improvements in lung function, mucociliary clearance, mucus rehydration and quality of life. The results of this study in combination with its European, Australian and New Zealand counterpart study seek to confirm these early findings and to extend the evidence to support its use as a mucoactive therapy for promoting bronchial hygiene in subjects with cystic fibrosis.

We hypothesize that inhaled mannitol will improve the overall health and hygiene of the lung through regular and effective clearing of the mucus load. On commencing treatment, we expect an acute clearance of the retained mucus and with twice daily use, ongoing mucus clearance to be associated with reduced mucus production. Acute clearance is cough assisted, however once the chest is cleared, patients should experience long cough free periods both during the day and following the evening treatment, at night. It is expected that this will be reflected as an improvement in health related quality of life.

In respect to the lung, we expect findings on auscultation to improve in line with respiratory function as a result of clearing blocked and impeded airways. As a consequence of the reduction in mucus load, exacerbations, and related antibiotic use should fall. Days in hospital and community health care costs are expected to change in line with improvements in respiratory health.

Finally, we plan to demonstrate that inhaled mannitol is safe and well tolerated over a 52 week period. We will test these hypotheses using 400 mg inhaled mannitol twice daily against control.

3 STUDY DESIGN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint:

- Change in absolute FEV_1

3.1.2 Secondary Endpoints:

Measures of Efficacy

- Change in absolute FEV_1(rhDNase group)
- Pulmonary exacerbations in those taking rhDNase as a sub-group and in the total cohort
- Quality of life scores using Cystic Fibrosis Questionnaire-R
- Rescue antibiotic use (number of agents course and days of use)
- Change in FVC, FEF_{25-75} from baseline
- Days in hospital due to pulmonary exacerbations

Measures of Safety

- Adverse events
- Laboratory safety tests: complete blood count, blood urea nitrogen, electrolytes, liver function tests
- Qualitative sputum microbiology
- Quantitative sputum microbiology for S. *aureus* and P. *aeruginosa*
- Physical examination findings

Assessment of Cost-Effectiveness

- Total costs incurred in intervention and control groups
    * Costs associated with inhaled mannitol
    * Cost of antibiotic use and rescue medication
    * Costs of hospitalizations and other secondary care services used
    * Cost of primary and community care services used
- Indicators of effectiveness and quality of life for intervention and control groups
    * As above
- Determination of cost-effectiveness ratios
- Sensitivity analysis
    * To assess extent to which variation in parameter estimates affect cost effectiveness ratios

3.2 General Design and Study Schema

This is a double blind, randomized, parallel arm, controlled, multi-center, interventional clinical trial. After satisfying all inclusion & exclusion criteria, subjects will be given a mannitol tolerance test (MTT). Those with a negative MTT result will be randomized to receive for 26 weeks, 400mg BID inhaled mannitol or control, in a ratio of 3 subjects to mannitol to 2 subjects to control (see Diagram 1). On completion of the blinded phase, subjects will move into a 26 week open label phase.

Diagram1. Study Schema

<table>
<tr><td>Screen ⇨ randomize</td><td colspan="3">26 week blinded phase</td><td colspan="2">26 week open phase</td></tr>
<tr><td rowspan="3">Active</td><td colspan="3">mannitol 400mg BID</td><td colspan="2" rowspan="5">mannitol 400mg BID</td></tr>
<tr><td colspan="3">mannitol 400mg BID</td></tr>
<tr><td colspan="3">mannitol 400mg BID</td></tr>
<tr><td rowspan="2">Control</td><td colspan="3">control BID</td></tr>
<tr><td colspan="3">control BID</td></tr>
<tr><td>2 weeks</td><td>6 weeks</td><td>8 weeks</td><td>12 weeks</td><td>12 weeks</td><td>14 weeks</td></tr>
<tr><td>V0</td><td>V1</td><td>V2</td><td>V3</td><td>V4</td><td>V5 V6</td></tr>
<tr><td></td><td>Phone call 2wks</td><td></td><td></td><td>Phone call 4 wks</td><td></td></tr>
</table>

Summary of Visit Procedures

This study consists of 5 study visits over 28 weeks for the base safety and efficacy study and an additional 2 visits over 26 weeks for the open label phase (see Appendix 3: Time and Events Schedule). The procedures to be undertaken at each visit are as follows:

3.2.1 Visit 0 - Screening

Each potential subject will be examined to determine eligibility for the study. The following activities will be performed at this visit:

- Obtain written informed consent - this must be obtained before any study-related procedures, including medication withholding requests, are undertaken. This may be done prior to V0.
- Review inclusion / exclusion criteria, including but not limited to:
  - pulmonary function tests (FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75})
  - urine pregnancy test (for females of child-bearing potential).
  - physical examination / vital signs
- Subject/parent to complete age appropriate Cystic Fibrosis Questionnaire (CFQ-R) and Health Utilities Index (HUI)
- Collect 2 x sputum samples (prior to MTT) 1) for quantitative microbiology (sent to central lab) and 2) qualitative microbiology (sent to local lab)
- Obtain demographic information:
  - date of birth
  - height and weight (no shoes)
  - race and gender
  - age at diagnosis
  - CFTR mutation (if known)*
  - previous diagnosis (by HRCT) of CF related bronchiectasis (yes, no, unknown)*
- Review and record concomitant medications for the previous 3 months

- Review medical history
- Premedicate with 4 puffs of albuterol from a metered dose inhaler (MDI) (360-400µg) (SABA)**
- Conduct mannitol tolerance test (MTT)
- Randomize eligible subjects
- Collect venous blood sample for blood urea nitrogen, electrolytes, liver function, complete blood count.

NB: There is no need to collect blood for ineligible subjects, therefore collect sample post MTT.

* Enter this data only if known and confirmed evidence is available. It is not a study requirement to undertake these procedures.

**SABA is to be used approximately 5 -15 minutes prior to MTT. The default SABA for this study is 4 x puffs albuterol (360-400µg). However, the subject's preferred alternative SABA may be used as an alternative premedication. Please record premedication details.

3.2.2 Visit 1

Visit 1 will occur 2 weeks post screening visit (+21days)

The following procedures will be performed:

- Review concomitant medications and adverse events
- Conduct physical examination including: chest sounds, weight, BP, HR, O_2 sat, temp, respiratory rate
- Medication withholding periods before spirometry must be complied with or subject should be postponed
- Perform pulmonary function testing (FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75}) (Baseline data)
- Collect 1 x sputum sample for qualitative microbiology (sent to local lab)
- Premedicate with 4 puffs of albuterol from a metered dose inhaler (MDI) (360-400µg) **
- Administer initial dose of study medication (mannitol/control) according to 'Study Drug Administration Procedure' (see section 3.3.19) and randomization group.
- Collect all sputum produced during and for 30 mins post study medication, then weigh collection.
- Perform 30 minute post dose FEV_1
- Dispense study medication according to randomization schedule
- Dispense bronchodilator.

** Short acting $beta_2$ agonist (SABA) is to be used approximately 5 -15 mins prior to each dose of study medication. The default SABA for this study is 4 x puffs albuterol (360-400µg). The subject's preferred SABA may be used as an alternative premedication. Care must be taken to ensure that a SABA is used prior to ALL mannitol/control treatments.

- Issue study diary and provide subject with thorough instructions on how to complete it

☎ Phone call 2 weeks after visit 1.

Two weeks into the blinded phase of the study, the investigator or designate, will call the participant to enquire as to their health with particular regard to response to study medication. If problems are noted and an unscheduled visit is deemed necessary, this should be arranged.

3.2.3 Visit 2

Visit 2 should occur on completion of 6 weeks study treatment (-7 to +14 days)

The following procedures will be performed:

- Medication withholding periods before spirometry must be complied with or subject should be postponed
- Review concomitant medications and adverse events
- Conduct physical examination including: chest sounds, weight, BP, HR, O_2 sat, temp, respiratory rate
- Perform pulmonary function testing (FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75})
- Pulmonary exacerbations review
- Medical resource use review (refer to study diary)
- Dispense study medications and bronchodilator
- Collect 2 x sputum samples for 1) quantitative microbiology (sent to central lab) and 2) qualitative microbiology (sent to local lab)
- Conduct drug accountability

3.2.4 Visit 3

Visit 3 should occur at the end of 14 weeks study treatment (±14 days)

The following procedures will be performed:

- Medication withholding periods before spirometry must be complied with or subject should be postponed
- Administer age appropriate Cystic Fibrosis Questionnaire (CFQ-R) and Health Utilities Index (HUI)
- Review concomitant medications and adverse events
- Conduct physical examination including: chest sounds, weight, BP, HR, O_2 sat, temp, respiratory rate
- Perform pulmonary function testing (FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75})
- Premedicate with 4 puffs of albuterol from a metered dose inhaler (MDI) (360-400μg)
- Administer subject's usual dose of inhaled mannitol/control in clinic
- Collect all sputum produced during and for 30 mins post study medication. Weigh collection.
- Perform 30 minute post dose FEV_1
- Collect 1 x sputum sample for qualitative microbiology (sent to local lab)
- Pulmonary exacerbations review
- Medical resource use review
- Dispense study medications and bronchodilator
- Conduct drug accountability

3.2.5 Visit 4

Visit 4 should occur at the end of 26 weeks of study treatment (±14 days)

The following procedures will be performed:

- Medication withholding periods before spirometry must be complied with or subject should be postponed

- Administer age appropriate Cystic Fibrosis Questionnaire (CFQ-R) and Health Utilities Index (HUI)
- Review concomitant medications and adverse events
- Conduct physical examination including: chest sounds, height, weight, BP, HR, O_2 sat, temp, respiratory rate
- Perform pulmonary function testing (FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75})
- Pulmonary exacerbations review
- Medical resource use review
- Collect blood sample for blood urea nitrogen, electrolytes, liver function, complete blood count
- Conduct drug accountability
- Conduct urine pregnancy test (females of child bearing potential only)
- Pre-medicate with short acting bronchodilator
- Administer initial dose of open label inhaled mannitol
- Perform post dose FEV_1
- Collect 2 x sputum samples for 1) quantitative microbiology (sent to central lab) and 2) qualitative microbiology (sent to local lab)
- Dispense study medications and bronchodilator
- Issue 2nd study diary if required

☎ Open label phone call at 4 weeks

Four weeks into the open label phase of the study, the investigator or designate, will call the participant to enquire as to their health with particular regard to response to the open label medication. If problems are noted and an unscheduled visit is deemed necessary, this should be arranged.

Open Label Visits

3.2.6 Visit 5

Visit 5 should occur at the end of 38 weeks of study treatment. (12 weeks post visit 4) (±14 days)

The following procedures will be performed:

- Medication withholding periods before spirometry must be complied with or subject should be postponed
- Review concomitant medications and adverse events
- Conduct physical examination including: chest sounds, weight, BP, HR, O_2 sat, temp, respiratory rate
- Perform pulmonary function testing (FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75})
- Pulmonary exacerbations review
- Dispense study medications and bronchodilator
- Collect 1 x sputum sample for qualitative microbiology (sent to local lab)
- Conduct drug accountability

3.2.7 Visit 6

Visit 6 should occur at the end of 52 weeks of study treatment (14 weeks post visit 5) (±14 days)

The following procedures will be performed:

- Medication withholding periods before spirometry must be complied with or subject should be

postponed
- Review concomitant medications and adverse events
- Conduct physical examination including: chest sounds, height, weight, BP, HR, O_2 sat, temp, respiratory rate
- Perform pulmonary function testing (FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75})
- Pulmonary exacerbations review
- Collect 1 x sputum sample for qualitative microbiology (sent to local lab)
- Collect blood sample for blood urea nitrogen, electrolytes, liver function, complete blood count
- Conduct drug accountability
- Collect diary
- Discharge subject from study

3.2.8 Early Withdrawal Assessments

Any subject withdrawing early from the study should be asked to contribute a blood sample (CBC, electrolytes, BUN, LFT) for safety follow-up, providing they have received at least 2 months of study medication. Where a visit is due, study procedures should be completed as far as practical. If withdrawal occurs between visits, the next study visit procedures should be conducted where practical. Drug collection, compliance and accountability should occur.

3.3 Study Procedures

3.3.1 Informed Consent

The Investigator will explain the benefits and risks of participation in the study to each subject, subject's legally acceptable representative or impartial witness and obtain written informed consent. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study related procedure and administration of study drug). When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative. The Sponsor will provide a sample informed consent form, based on the elements of informed consent, Appendix 2. The final, version dated, form must be agreed to by the Sponsor and the IRB and will contain all elements in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject or by the subject's legally acceptable representative, and by the physician conducting the informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled subjects with a copy of their signed informed consent and assent where appropriate

The consent form may need to be revised during the trial should important new information become available that may be relevant to the safety of the subject. In this instance approval should always be given by the IRB and existing subjects informed of the changes and reconsented. This is documented in the same way as previously described.

The Investigator should with the consent of the subject or subject's legally acceptable representative, inform the subject's primary physician about participation in the clinical trial.

3.3.2 Eligibility Criteria

Applies to V0

Subjects will be reviewed for eligibility against the study inclusion and exclusion criteria.

3.3.3 Medical History

Applies to V0

A comprehensive medical history will be undertaken by the investigator to determine past and current medical conditions and procedures. Note will be made of the presence or absence of bronchiectasis (only if previously been physician diagnosed) and the subjects CF mutation (if already known)

3.3.4 Demographic Information

Applies to V0

The following information will be collected: date of birth, height and weight, race, gender, age at diagnosis.

3.3.5 Concomitant medications

Applies to V0 with updates every visit thereafter.

Medication use, current, and in the preceding 3 months will be noted. Generic names are to be used where possible, though trade names may be used for combination drugs. Start and stop dates, total daily dose, route and indication for use should be recorded. "Alternative or homeopathic therapies" are not to be recorded in the CRF.

Where possible the use of all concomitant medications at the start of the treatment period should be maintained throughout the treatment period, and wherever possible, institution of new concomitant medications should be avoided.

Hypertonic saline (HS) should not be used during the study. Those using HS at screening, and wishing to take part in the study, must have a 4 week washout period prior to visit 1.

Beta blockers may interfere with $ß^2$ agonists and therefore are contraindicated during this study. Alternative medications to beta blockers to treat hypertension should be considered by the treating physician.

3.3.6 Physical Examination and Vital Signs

Applies to all visits

A physical examination must include as a minimum:

Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation, temperature), chest auscultation, height and weight. The physical examination should be conducted by a physician, but where timing prohibits this, a suitably trained nurse or respiratory therapist may undertake this task. If any doubt exists about the physical status of the subject (including determining exacerbations and respiratory tract infections), the physician should be consulted.

3.3.7 Spirometry

Applies to visits 0 – 6 inclusive

All study spirometry must be conducted according to the ATS/ERS criteria 2005[31]

3.3.7.1 Patient Considerations

Where possible, pulmonary function testing should be performed as close as possible to the same time of the day at each visit. All visits should coincide with the trough treatment effect i.e. approximately 6 - 12 hours since the previous medication dose. The order and timing of all concurrent treatments e.g. postural drainage and medications, and required withholding of concurrent medications should be the same for

every visit.

All pulmonary function testing should be done in the sitting position, unless the subject is obese, who will commonly obtain a deeper inspiration when tested in the standing position.

Subjects should avoid the activities listed before lung function testing;

- smoking within 1 hour of testing
- consuming alcohol within 4 hours of testing
- performing vigorous exercise within 30 min of testing

The medications listed in Table 1 must be withheld prior to all spirometry (visit 1 onwards)

Subjects who fail to withhold medications as directed must be rescheduled.

Table 1: Medication Withholding Periods

Medication	Minimum time interval from last dose until spirometry
Inhaled mannitol/control	6 to 12 hours
Short acting bronchodilators (isoproterenol, isoetharine, metaproterenol, albuterol, levalbuterol, terbutaline) (e.g. Proventil® or Ventolin®)	6 hours
Inhaled anticholinergics or combination products (e.g. Atrovent® or Combivent®)	12 hours
Long acting β agonists *eg salmeterol; efomoterol*(e.g. Serevent® or Foradil®)	12 hours
Medium acting bronchodilators eg. Ipratropium	12 hours
Oral bronchodilators eg. Theophylline and β-agonist tablets	12 hours
ICS LABA combinations *eg fluticasone and salmeterol, budesonide and efomoterol*(e.g. Advair®)	12 hours

3.3.7.2 Limitations of Methodology/Validation of Results

Spirometry is an effort-dependent test that requires very careful instruction and cooperation of the test subject. Inability to perform acceptable maneuvers may be due to poor subject motivation or failure to understand instructions. Physical impairment and young aged children (e.g. children <6 years of age) may also limit the subject's ability to perform spirometric maneuvers. These limitations do not preclude attempting spirometry, but should be noted and taken into consideration when the results are interpreted.

The results of spirometry testing should meet the ATS/ERS criteria (as follows) for number of trials, acceptability, and repeatability. The acceptability criteria should be applied before repeatability is checked.

Number of trials: A minimum of 3 acceptable FVC maneuvers should be performed. If a subject is unable to perform a single acceptable maneuver after 8 attempts, testing should be discontinued. However, after additional instruction and demonstration, in some cases more maneuvers may be performed depending on the subject's clinical condition and tolerance.

Acceptability: A good 'start-of-test' includes:

- An extrapolated volume of ≤5% of the FVC or 150 ml, whichever is greater
- No hesitation or false start
- A rapid start to rise time (e.g. a short peak expiratory flow time)

Acceptability: No cough, especially during the first second of the maneuver.

Acceptability: No early termination of exhalation:

- A minimum exhalation time of 6 seconds (3 seconds for children) is recommended, unless there is an obvious plateau of reasonable duration (e.g. no volume change for at least 1 second) or the subject cannot or should not continue to exhale further
- No maneuver should be eliminated solely because of early termination. The FEV_1 from such maneuvers may be valid, and the volume expired may be an estimate of the true FVC, although the FEV_1/FVC and FEF_{25-75} may be overestimated

Repeatability: Two highest FVCs within 0.150 L, Two highest FEV_1s within 0.150 L. Or if FVC < 1.0 L, then FVC and FEV_1 repeatability to be better than 0.100 L.

Quality Control

To facilitate quality spirometry, the following will be implemented:

- Regular review of spirometric measures will be performed and feedback will be provided to sites.
- Standardized spirometers that meet ATS/ERS requirements must be used.
- All lung function measures as they apply to this study will be performed on a dedicated spirometer. Each subject should be measured on the same spirometer at each visit at approximately the same time of day.
- Predicted tables will be standardized across sites.
- All personnel performing spirometry must be trained, experienced and qualified to do so.

3.3.7.3 Reporting of Spirometry Results

- The largest FVC and FEV_1 (at body temperature, ambient pressure, saturated with water vapor, (BTPS)) should be reported even if they do not come from the same curve.
- Other reported measures (e.g. FEF_{25-75} and instantaneous expiratory flow rates, such as FEF_{max} and FEF_{50}) should be obtained from the single acceptable 'best-test' curve (e.g. largest sum of FVC and FEV_1) and reported at BTPS.
- All values should be recorded and stored so that comparison for reproducibility and the ability to detect spirometry induced bronchospasm (as evidenced by a worsening in spirometric values with successive attempts and not related to fatigue) are simplified.
- The time of day, equipment or instrumentation used, beginning and end times of tests and name of the technician administering the test should be recorded.
- Flow volume curves should be printed for data verification.

3.3.7.4 Selecting Spirometry for Data Entry into the CRF

The following spirometry results demonstrate how site staff will select the correct data:

Time	Effort	FEV_1	FVC	FEV_1/FVC%	FEF_{25-75}	PEF
10.48	1	2.45	3.70	66	1.75	6.7
10:50	2	2.33	3.69	63	1.70	6.0
10.52	3	2.41	3.76	64	1.79	6.5

The results that must be used in analysis are:

- **FEV_1**: 2.45 (best individual result)
- **FVC**: 3.76 (best individual result)
- **PEF**: 6.7 (best individual result)
- **FEV_1/FVC%: 2.45 / 3.76 = 65** (best individual FEV_1 / best individual FVC (may be from

separate efforts)

- **FEF_{25-75}: 1.79** (from the effort with the highest FVC+FEV_1) - see below for example:
  Effort 1: 2.45 + 3.70 = 6.15
  Effort 2: 2.33 + 3.69 = 6.02
  Effort 3: 2.41 + 3.76 = 6.17 (record value of 1.79)

All of the above are from acceptable efforts. The best single effort will be determined based on the highest combined value for FEV_1 and FVC.

3.3.7.5 Adult and Child Predicted Tables

Predicted values for all spirometry will be based on the Wang[32]and Hankinson[33] (NHANES III) predicted tables. Adjustments for race should be used when determining normal predictive values. Note that there is considerable age overlap between Wang and Hankinson, therefore, Wang shall only be used for children < 8 years, while Hankinson (NHANES III) will be used for everyone ≥8 years old.

For Non-Caucasian subjects, a 12% reduction will be used.

Example: Hankinson predicted FEV_1 = 3.0L. Adjusting for Non-Caucasian race at 88%, (0.88*3.0), = 2.64L.

3.3.8 Mannitol Tolerance Test (MTT)

Conducted at visit 0

The MTT procedure identifies subjects who have airway hyperresponsiveness in response to inhaled mannitol. Airway hyperresponsiveness is determined by measuring the degree of bronchoconstriction that occurs following sequential administrations of D-mannitol.

3.3.8.1 Safety Guidelines and Equipment Requirements

As is standard in administering agents that have the potential to cause bronchoconstriction, a physician, appropriately trained to treat acute bronchospasm, including the use of resuscitation equipment, must be available to respond to an emergency.

As a minimum, the person conducting the MTT procedure must:

- Be competent, qualified and experienced in performing bronchial provocation tests
- Be familiar with safety and emergency procedures
- Know when to stop further testing
- Be proficient in the administration of inhaled bronchodilators and other rescue medications and equipment
- To maintain blinding, the person conducting the MTT and the study coordinator should not be the same person

The following equipment should be available during the MTT procedure:

- MTT kit with Osmohaler-HR
- Bronchodilator metered-dose inhalers and spacers
- A spirometry system that meets ERS/ATS requirements.
- Calculator and 60 second timer
- Pulse oximeter
- Epinephrine, atropine and oxygen

3.3.8.2 Monitoring Subject Safety during the MTT Procedure

Subjects should be monitored during the MTT procedure by following the schedule listed in table 3.

Table 3: Safety Monitoring During the MTT Procedure

Parameter	Baseline (pre- bronchodilator)	At each dose step	At steps 4, 5 and 6	15 min post test *
SpO_2	X	X		X
FVC	X			X
FEV_1	X		X	X
Clinical signs &symptoms		X		X

* Post test FVC should be measured for all patients including those with +ve tests, -ve tests and incomplete tests

3.3.8.3 MTT Technical Considerations

- The gelatin capsules may fragment if pierced more than once.
- Inhale from device in a deep controlled manner at a rate fast enough to make the capsule spin and empty
- A 5 second breath hold should follow each capsule inhalation
- A 2nd inhalation may be required if the capsule appears not to have emptied
- To facilitate the development of an osmotic gradient within the airway, there should be minimal delay between sequential doses.
- Static charge can be problematic with dry powders, particularly in low humidity environments. If the capsule fails to spin in the device on inhalation, tilt the device mouthpiece down and firmly tap the base to drop the capsule into the spinning chamber.
- Cough may be controlled by slowing the rate of inhalation, while still ensuring that the flow rate is enough to facilitate emptying the capsule. Cough may lessen with subsequent administrations.
- Water can be given following the procedure to clear residual powder from the oropharynx.
- The subject should never exhale into the device.

3.3.8.4 When to Stop the MTT Procedure

Stop the MTT procedure if:

- The subject's oxygen saturation falls below 89% (record as an adverse event)
- Cough is highly distressing or vomiting occurs (record as an adverse event)
- Subject's FEV_1 has fallen $\geq$20% (from baseline) at step 4 or 5 of the procedure
- A total of 400mg inhaled mannitol has been administered
- Clinical signs and symptoms are causing concern

3.3.8.5 MTT Procedure

1. Perform baseline spirometry and measure SpO_2. Multiply the patient's best FEV_1 by 0.80 and 0.50 to obtain the 20% and 50% fall in FEV_1 values respectively.
2. Premedicate patient with 4 x puffs albuterol* and wait 5–15 min
3. Administer the MTT as follows:
   - inhale contents of 1x 40mg capsule in a controlled, deep inhalation; breath hold for 5 seconds, then exhale
   - wait 60 seconds, then measure $Sp0_2$

   If $Sp0_2$<89%, discontinue test and treat as required, otherwise go to step 4

4. Administer an additional 80mg MTT (2 x 40mg) as above; wait 60 seconds, then measure FEV_1 & $Sp0_2$

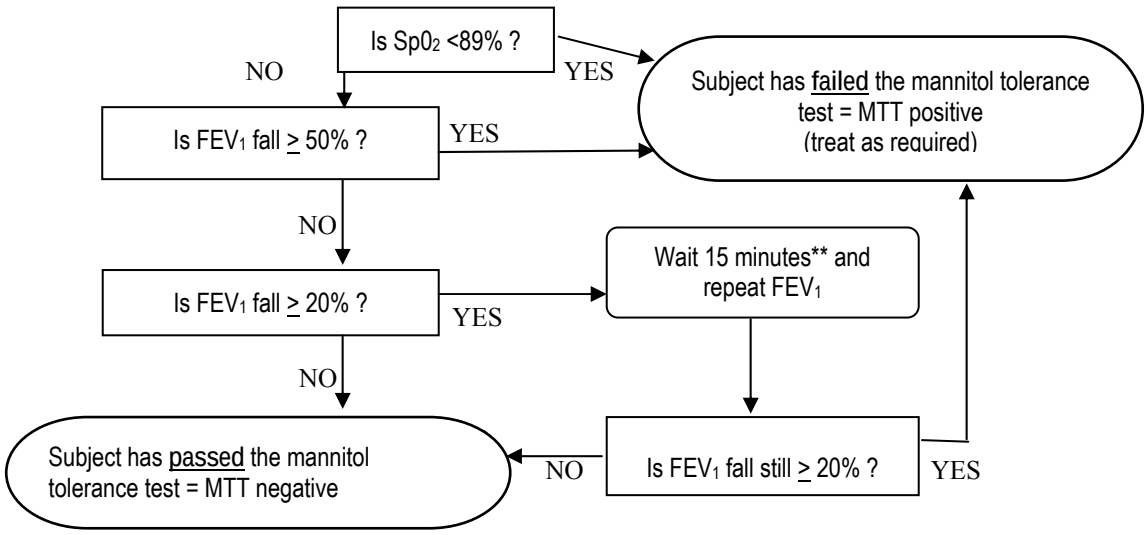
   If FEV_1 fall is ≥20% (from baseline) or SpO_2 <89%, discontinue test and treat as required, otherwise go to step 5

5. Administer an additional 120mg MTT (3 x 40mg) as above. Wait 60 seconds, measure FEV_1 & $Sp0_2$

   If FEV_1 fall is ≥20% (from baseline) or SpO_2 <89%, discontinue test and treat as required, otherwise go to step 6

6. Administer an additional 160mg MTT (4 x 40mg) as above. Wait 60 seconds, measure FEV_1 & $Sp0_2$.

   Assess **step 6** (only) as follows:



7. 15 minutes post test, measure recovery spirometry (irrespective of result or when the test was terminated).

* alternative short acting bronchodilator may be used
** consider using PEP mask /Acapella/ cough clearance to facilitate airway opening.

MTT Assessment

The MTT procedure should be assessed as follows:

MTT Positive Test

1. The subject's oxygen saturation falls below 89% (record as adverse event)
2. Subject's FEV_1 has fallen $\geq$20% (from baseline) at step 4 or 5
3. Subject's FEV_1 has fallen $\geq$20% (from baseline) at step 6 and does not return to <20% within 15 minutes
4. Subject's FEV_1 has fallen $\geq$50% (from baseline) at step 6

MTT Negative Test

1. A total of 400mg MTT has been administered (and no positive criteria have been met)
2. Subject's FEV_1 has fallen $\geq$20% (from baseline) at step 6 and has returned to <20% within 15 minutes

MTT Incomplete Test

1. Cough is highly distressing or vomiting occurs during the procedure (record as adverse event)
2. Any other reason not listed above where test is incomplete

Caution

If the subject shows clinical signs and symptoms of bronchoconstriction e.g. wheeze, dyspnea, shortness of breath; measure FEV_1 and treat accordingly.

3.3.9 Pregnancy Testing

Applies to visits 0 and 4

Pregnancy tests will be performed using a standard urine test at screening and at V4, on all women of child bearing potential. Subjects who are pregnant are excluded from the study. Female subjects who are at risk of becoming pregnant are expected to prevent pregnancy occurring whilst on treatment by using effective birth control methods e.g. oral contraceptive, condom, IUD, injectable contraceptive, diaphragm. Male subjects have no contraceptive restrictions as they pertain to this study medication.

The investigator will inform the Sponsor immediately of any case of pregnancy and collect information on any subject who becomes pregnant during the study. Pregnant subjects will discontinue treatment but will continue to be followed up for scheduled safety assessments for the duration of the study. Subjects will also be followed to determine the outcome of pregnancy.

3.3.10 Cystic Fibrosis Questionnaire - Revised

Applies to visits 0, 3 and 4

The Cystic Fibrosis Questionnaire (CFQ-R)[34] is a validated, disease specific, developmentally appropriate questionnaire designed to measure the physical, emotional and social impact of CF on patients and their families. It should be administered in a quiet room prior to other study related procedures where possible. The following formats apply:

* Ages 6 – 11: Administered by an interviewer
* Ages 12-13: Self report format
* Ages 14 and over: Self report format
* Parent version: For parents of children aged 6 – 13 years. This is completed in addition to the

child's questionnaire.

If a child has a birthday anytime between visit 0 and visit 4 that promotes them into an older age category e.g. a 13 year old turns 14, that child should continue to complete the original format questionnaire e.g. 12 -13 years format. The parent of that child should continue to complete the Parent version. (Sample CFQ-R Appendix 4)

3.3.11 Health Utilities Index

Applies to visits 0, 3 and 4.

The Health Utilities Index (HUI) is a generic, preference scored, comprehensive system for measuring health status, health related quality of life and producing utility scores. The HUI is self administered for subjects aged ≥12 years and proxy administered for children <12 years old. HUI scores will be used to develop Quality Adjusted Life Years (QALY) which will only be used in the cost effectiveness analysis. (Sample HUI Appendix 5)

3.3.12 Blood Samples

Applies to visits 0, 4 and 6.

Subjects will be asked to provide a venous blood sample to be analysed at the institutional laboratory for a complete blood count, liver function tests (AST, ALT, total bilirubin, Alkaline phospatase, GGT and indirect bilirubin) and electrolytes, blood urea nitrogen. The V0 blood sample should only be collected from MTT negative subjects.

Sites will provide a list of reference ranges from the laboratory conducting these tests. To minimize the discomfort associated with needle sticks in children, a topical anesthetic may be applied at an appropriate time prior to blood draws.

3.3.13 Abnormal Blood Results

Results outside reference ranges post screening, will be listed as adverse events providing they were not present at visit 0 and the abnormality is determined to be clinically significant by the investigator. Note must be made in this regard in the medical record. Clinically significant abnormal results detected at visit 0 will be listed as a pre-existing medical condition. Additional and repeat laboratory safety testing may be performed at the discretion of the investigator.

3.3.14 Sputum Collection for Qualitative and Quantitative Microbiology

Applies to visit 0 through 6 inclusive (qualitative) and visits 0, 2, 4 (quantitative)

Note: The Visit 0 microbiology sputum samples should be taken **before** administration of the MTT procedure and will represent the baseline sample. **Nebulized normal or hypertonic saline should NOT be used to induce sputum.**

Subjects who are unable to produce spontaneous sputum sample for microbiology should be given postural drainage and percussion, deep breathing and coughing exercises to encourage sputum production.

Sputum samples for qualitative microbiology only, may be collected at home prior to the study visit if providing sputum on demand is problematic. Samples collected at home should not be greater than 24 hours old and must be refrigerated at all times. Sterile sample containers should be given to subjects for at home collections. For samples collected at home, the following applies:

- collect samples as close as possible to the next clinic visit and refrigerate

- collect in sterile sample containers and label with collection date, time and name
- transport sample in an insulated container with ice brick to clinic

As a substitute for **qualitative** microbiology only, sputum samples that cannot be collected as above, should be collected as an oropharyngeal throat swab (see directions below). **Qualitative Microbiology Collection Procedure (local lab processing)**

Sputum Sample Collection Procedure

1. Provide the subject with 1 cup of water and 1 empty cup. Ask the subject to rinse and gargle and spit in empty cup (x3). This will eliminate squamous cell contamination of the specimen
2. Dispose of cup, subject may retain a cup of water to drink during the procedure
3. Instruct and demonstrate how to obtain sputum from the lungs by coughing and clearing the throat (deep cough and hack!)
4. Ask subject to cough, clear their throat and deposit all or any oral contents into the specimen container. Listen to the subject to ensure the sample is from the lungs and not post nasal secretions
5. Wear gloves. Open the specimen cup and collect the sputum sample directly into the open cup. Unscrew the cover on the specimen cup and place the lid, face up, on a flat surface. Do not touch inside the lid or the inside of the open specimen cup. Cough deeply to bring up sputum from the lung. Spit the sputum specimen directly into the specimen cup. Do not contaminate the outer surfaces of the specimen cup with sputum. After you have collected the sputum sample in the specimen cup, replace the lid. Seal the lid securely to prevent leaking.
6. Once an adequate specimen has been obtained, label the specimen jar as per protocol (including name, date and time as a minimum), place in specimen bag and refrigerate immediately.
7. Contact local lab staff for immediate pick up of specimen
8. Sample should be cultured locally and reports reviewed by the investigator. Results should be recorded in the CRF.

Oropharyngeal Throat Swab Collection Procedure (not to be used for quantitative micro)

1. Use a sterile pre-packaged culture swab with transport media to obtain the oropharyngeal specimens
2. Depress the tongue to adequately expose the oropharynx
3. The swab must be rubbed over the posterior pharynx and over each tonsillar area. Rotate the swab over each area for a total of 3-5 seconds. Any area with exudate should also be touched.
4. Care should be taken to avoid contaminating the swab by touching the tongue or lips
5. Reinsert the swab stick into the sheath and label (including name, date and time as a minimum), place in specimen bag and refrigerate immediately
6. Contact local lab staff for immediate pick up of specimen
7. Sample should be cultured locally and reports reviewed by the investigator. Results should be recorded in the CRF.

Quantitative Microbiology Collection Procedure (central lab processing)

Samples for quantitative microbiology must be collected freshly expectorated, refrigerated (not frozen) and immediately shipped to the central lab for processing. Samples must be <48hours old on arrival in the central lab. A minimum of 1mL is required for quantitative processing. Samples will be processed according to a standardized protocol (refer to laboratory manual for details). Oropharyngeal swabs **are not suitable** for quantitative processing.

1. Collect sputum sample following steps 1 – 6 for “sputum samples” as above.

2. Immediately ship to the central laboratory in a temperature monitored cold pack to arrive within 48 hours of expectoration. DO NOT FREEZE / DO NOT USE DRY ICE. Refer to the laboratory manual for shipping instructions.

3.3.15 Antibiotic Use

The use of rescue antibiotics is an outcome measure and as such must be carefully monitored and documented. This will include all nebulized antibiotics, oral and intravenous use. Subjects will be asked to keep a diary record of all antibiotic use while in the study. This will include the antibiotic name, indication for use, the dose and the start and stop dates. Study coordinators will track all antibiotic use, noting the diary records as well as outpatient clinic and hospital records. Routine antibiotic use will be distinguished from rescue antibiotics.

3.3.16 Pulmonary Exacerbations

A protocol defined pulmonary exacerbation occurs when subjects are treated with **intravenous** antibiotics for **four or more** of the following twelve signs or symptoms[12]:

1. change in sputum production (volume, color, consistency)
2. dyspnea
3. new or increased hemoptysis
4. malaise, fatigue or lethargy
5. fever ($\geq 38^{o}C$)
6. anorexia or weight loss
7. sinus pain or tenderness
8. change in sinus discharge
9. FVC or FEV_1 decreased by >10% from previous recorded value
10. radiographic signs indicative of pulmonary infection
11. increased cough
12. changes in physical examination of the chest

Pulmonary exacerbations are expected to occur as part of the disease but will be recorded as adverse events. Expedited reporting of serious exacerbations to Regulators and Ethics Committees will only be carried out if the exacerbation is considered to be related to study drug and is clinically different to that normally expected in a particular subject (e.g. more severe). In such cases, the difference should be noted on the AE form.

During regular clinic visits, subjects will be asked about their respiratory symptoms for an exacerbation update and history. Details will be collected on symptoms since the last visit and verbal information will be cross referenced to diary entries and antibiotic use.

3.3.17 Hospitalizations

If a subject is formally admitted to hospital this is considered to constitute a serious adverse event and as such a 'serious adverse event' form is completed. The only exceptions to this are hospital admissions that are pre-planned for elective procedures e.g., laser eye surgery, PEG replacement, cosmetic procedures, or are conducted on a regular and routine basis e.g. CF "tune up".

"Hospital in the home" or an equivalent program; or attendance / observation in the emergency department is not considered to be a hospital admission. Medications administered as part of any elective procedure or hospital in the home process, are to be recorded as concomitant medications.

3.3.17.1 Hospital Admission

At the time of hospital admission, the following information will be recorded if available:

- physical examination and medical history
- signs and symptoms checklist
- sputum microbiology results
- spirometry
- number of days since last hospital admission
- results of laboratory tests
- chest x ray report

3.3.17.2 Hospital Discharge

In addition to information recorded as per hospital admission, at the time of hospital discharge the following information must be obtained as close as possible to the discharge date.

- medications during admission
- number of days in hospital

3.3.18 Medical Resource Use

Subjects will be asked to log visits to health care practioners and institutions and health care services use into a study diary. Sites will be asked to provide instruction to subjects regarding completion and then to review this information at each visit for completeness.

Information to be collected will include:

* pharmaceutical use
* community visits to physicians, nurses, physiotherapists or other health care professionals
* hospital visits including overnight admissions, day case and outpatient.
* resources will be recorded from medical records, discharge summaries and subjects' diaries.

Analyses:

A standard costing method will be applied to assess the total health care cost from a community-health-service and hospital perspective. Subject's personal costs will be excluded. Included in the assessment will be: hospital admissions (inpatient, outpatient, day case); radiological investigations, blood tests, medication use, and the use of community services (e.g. visits to physicians, district nurses and physiotherapists).

Unit costs will be obtained from finance departments at the hospitals involved in the study and a district general hospital. Costs, both resource and unit, will include health professionals' time, consumables and overheads. Costs will be derived from documents such as USP-NF; Current Procedural Terminology from the American Medical Association; the Medicare Coverage Database or as nationally appropriate for other countries, and community care costs from published data

The Health Utility Index value will only be used to develop Quality Adjusted Life Years (QALY). The change in HUI value induced by the treatment will be multiplied by the duration of the treatment effect to provide the number of QALYs gained. QALY's will be incorporated with medical costs to arrive at a final common denominator of cost/QALY. This parameter will be used to compare the cost-effectiveness of mannitol with control.

Sensitivity analysis using cost and resource use data and effects and HUI data will also be undertaken.

3.3.19 Study Drug Administration Procedure

Standard Rules for Administering Mannitol / Control

- Always Pre-medicate with 4 puffs of albuterol from a metered dose inhaler (MDI) (360-400μg) or the subject's preferred short acting bronchodilator alternative. Wait 5 – 15 minutes for the bronchodilator to take effect. Record pre-medication details.
- Load capsule into the inhaler device
- Puncture the capsule once only (a second puncture may shatter the capsule)
- Never exhale into the device
- Inhale from device in a deep controlled manner at a rate fast enough to make the capsule spin and empty (training kits are provided with empty capsules)
- A 5 second breath hold should follow each capsule inhalation
- A 2nd inhalation may be required if the capsule appears not to have emptied
- Wash residual medication from the mouth by drinking water after treatment
- Administer capsules in rapid succession so osmotic effect is cumulative
- Keep all empty blister packs and any unused capsules and return to clinic for compliance checks

Subjects will be given bronchodilator to take home to be used as pre-medication before every study treatment (with inhaled mannitol/control), which may also be used in the event that they experience chest tightness post treatment. The pharmacist is responsible for dispensing the bronchodilator, while the investigator is responsible for instructing the subject in the use of the bronchodilator inhaler and the correct mannitol / control administration procedure. To ensure good delivery technique, training kits containing empty capsules, are provided. An alternative short acting bronchodilator may be used if the subject does not tolerate albuterol. Children may benefit from the use of a spacer when administering MDI bronchodilators.

Study medication should be taken twice a day, once in the morning and once in the evening, approximately 2 hours before sleep and ideally within 30 minutes before the subject's physiotherapy session. If the subject is unable to attend for follow up assessment on due visit date, additional medication has been included in each supply to allow for a delay of 14 days in each study period. Subjects should attend for assessment before the last treatment is used. Subjects should bring in all used and unused blisters at each assessment visit to check for compliance. Empty, used capsules should be thrown away.

Study medication must not be refrigerated nor kept in humid conditions such as bathrooms. It should be stored at room temperature in a clean, dry environment. Capsules should be carefully removed from the foil packaging only just prior to use.

3.3.20 Administration of Treatment Dose in Clinic at Visit 1, 3 and 4

Applies to visit 1, 3 and 4

Following the "standard rules for administering mannitol/control" (Section 3.3.19) , study staff will administer the visit 1, visit 3 and visit 4 dose of study medication in the clinic according to the following plan:

1. Perform **pre-bronchodilator** spirometry (if not already done)
2. Pre-medicate with short acting bronchodilator as above
3. Administer dose of prescribed study medication as above
4. Collect ALL sputum produced during the procedure into a pre-weighed specimen jar. The entire sample collected during and for 30 mins post dose will be weighed using the study scales, and recorded. This 30 minute sputum collection applies to Visit 1 and 3 only.
5. Measure FEV_1 30 minutes post dose completion.

If the subject has a measured fall in FEV_1 $\geq$20% at 30 minutes post dose completion, no further study medication should be administered. The subject should be continued in the study on an intention to treat basis. Symptomatic bronchoconstriction should be managed as medically appropriate.

3.4 Open Label Period

The purpose of the open label period is to obtain data on the long term safety and tolerability of inhaled mannitol and to give those subjects randomized to the control arm exposure to the active treatment.

3.5 Time Schedule and Accrual Procedures

Subject accrual is expected to occur at an average rate of 1 subject every month per center. Subject enrolment will end when recruitment goals are met unless the study is terminated early or attrition rates are beyond expected or recruitment rates are slower than expected, whereby the recruitment period will be extended. The investigator(s) should make every effort to ensure that the planned accrual rate is maintained, that eCRFs are completed promptly and completely, and that data quality is maintained at all times. The investigator(s) should discuss with the monitor any anticipated problems with recruitment or delays in study completion.

3.6 Randomization and Blinding

- Subjects failing to meet any of the inclusion/exclusion criteria, with the exception of MTT status, will not be entered onto the eCRF but will be entered onto the site screening log
- Only subjects who are administered the MTT should be entered onto the eCRF. This should occur irrespective of the MTT result and all such subjects will be allocated an enrollment number
- Only subjects with a negative MTT result will be randomized to a treatment group. Those with a positive MTT will not proceed in the study but their data for visit 0 will be collected.
- Three subjects will be randomized into the inhaled mannitol arm for every two subjects allocated to control
- Randomization will be managed by an interactive voice response system (IVRS)
- Generally 2 weeks will be allowed to prepare the randomized product for dispensing.
- The pharmacist will dispense the randomized treatment allocated to the subject to the study coordinator who will administer the initial dose to the subject at visit 1
- Both the subject and the investigative staff will be blinded to the treatment allocations
- The study pharmacist will hold the IVRS unblinding activation codes. Activation of the code should be done following consultation with Pharmaxis and only for a serious adverse event or emergency where the event or emergency is considered to be study drug related. All efforts should be made to contact Pharmaxis before any randomization code is broken.

Note that subjects will be included if there are any mismatches in randomization selection and treatment dispensing - but careful consideration will be given to the number of cases and effect of this on the findings.

3.7 Duration of Subject Participation

The total study duration for each participant will be 54 weeks, and includes a screening visit and 6 scheduled visits. The treatment period is 26 weeks long followed by a 26 week open label phase. Visit 1 will follow V0 by two weeks and visits 2, 3, 4, 5 and 6 will be 6, 8, 8, 12 and 14 weeks apart respectively. Progress phone calls will be made by the investigator to subjects 2 weeks following visit 1 and 4 weeks following visit 4.

3.8 Stopping Rules and Discontinuation Criteria

Subjects will be discontinued from the study in the following circumstances:

- Subject withdraws consent
- Positive MTT
- The Investigator decides that the subject should be withdrawn. If this decision is because of a serious adverse event, further administration of the study drug should be ceased and appropriate measures taken. The Sponsor (or representative) and the IRB/IEC are to be notified immediately
- The subject's attending physician requests that the subject be withdrawn from the study
- The Investigator or the Sponsor, for any reason, stops the study or stops the subject's participation in the study
- The subject is inadvertently enrolled but does not meet the enrolment criteria
- Pregnancy (discontinue treatment, continue monitoring)
- Non compliance with study medication or poor visit attendance

3.9 Study Drug Supply and Accountability

Each Investigator is responsible for ensuring that deliveries of study drug(s) and other study materials from the Sponsor are correctly received and recorded, that these materials are handled and stored safely and properly, and that they are used in accordance with this protocol.

Unused study drug(s) (opened, unopened, or empty blisters) must either be returned to the Sponsor or destroyed on site only after any discrepancies have been investigated and satisfactorily explained and fully reconciled by the Sponsor. Approval to destroy drug must be given in writing by the Sponsor prior to destruction. A list of study drug(s) and other materials received, used, returned, or destroyed must be prepared and signed by the Principal Investigator; and an account must be given for any discrepancies.

The site pharmacy will be responsible for storage and dispensing of the mannitol/control while the study coordinator will be responsible for storage and dispensing of the MTT kit, unless institutional requirements require otherwise.

All investigational drugs must be accounted for at the beginning, during and completion of the study. Pharmacy will be supplied with an instructional study manual.

3.10 Source Data and the Case Report Form

In this study the case report form will be an electronic Case Report Form (eCRF), built on an electronic data capture platform. The eCRF is fully compliant with 21CFR Part 11. It has full technical support for electronic signatures and contains all functionality required for electronic records retention. The database (including full audit trail, CRF and user data) and all versions of the software will be retained to ensure data retrieval at later dates and data for each site will be provided to that site for long term archival. The eCRF will display an identification number corresponding to the number of the centre and the subject enrolment number. The derived data, not containing any subject identifiers, will be provided to the Sponsor at the end of the study.

A full identification list of each participant will be kept by the Investigator who must agree to supply all details to Sponsor auditor(s) and/or regulatory authorities. The information will be treated in compliance with professional confidence and government regulations.

The Investigator or the designated site person must agree to complete the eCRF at each subject visit, and all other documents provided by the Sponsor (documents recording subject study participation). All corrections and alterations of data on the eCRF must be made by the Investigator or by the designated site person according to the instructions provided. All persons appointed by the Investigator to participate in the study must be indicated on the delegation of authority log.

Each Investigator or site designee will be assigned a unique user name and password associated with his or her name. The user name and password combination will be used to sign the eCRF at each visit, attesting to authenticity of the data collected in the case report form and agreement between the data in the case report form and those in the source documents.

In the case of withdrawal of consent or early termination by a participant, the Investigator or sub-Investigator will complete the study completion/withdrawal page, indicating the reason for early termination. Study completion will also be recorded and signed electronically. The entry of the Investigator or sub-investigator's user name and password combination will be considered the equivalent of a written signature. The following statement will appear with the electronic signature: "I affirm by my electronic signature above that I have reviewed all of the information on all pages/forms of this case report form and assume responsibility for the accuracy and completeness of the data."

The study will be monitored to make certain that all data are completed accurately on the eCRF as can be determined by a monitor at the site. Requests for correction/clarification will be submitted to the Investigator by the monitor or data manager when inconsistencies are identified during monitoring and source data verification or during the edit check process. The Investigator or designee will make the corrections in the system and submit the eCRF pages once again. The monitor or data manager will approve the corrections made in the system.

Any data recorded directly on the eCRF, for which no other written or electronic record exists in the subject's medical record, will be considered source data (e.g. results of physical examinations, vital signs testing, or the drug administration procedure) and will be provided to the site in an electronic format at the end of the study.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Subject Inclusion Criteria

Subjects may be included in the study if all of the following criteria are met. The subject must:

1. Have given written informed consent to participate in this study in accordance with local regulations
2. Have a confirmed diagnosis of cystic fibrosis (positive sweat chloride value ≥ 60 mEq/L) and/or genotype with two identifiable mutations consistent with CF, accompanied by one or more clinical features consistent with the CF phenotype)
3. Be aged ≥ 6 years old
4. Have FEV_1 ≥40 % and < 90% predicted (using Wang[32] <8 years and NHanes III[33] ≥8years)
5. Be able to perform all the techniques necessary to measure lung function

4.2 Subject Exclusion Criteria

Subjects are excluded from participating in this study if one or more of the following criteria are met. The subject must NOT:

1. Be investigators, site personnel directly affiliated with this study, or their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biologically or legally adopted.
2. Be considered "terminally ill" or eligible for lung transplantation
3. Have had a lung transplant
4. Be using nebulized hypertonic saline in the 4 weeks prior to visit 1*
5. Have had a significant episode of hemoptysis (>60 mL) in the three months prior to enrolment
6. Have had a myocardial infarction in the three months prior to enrolment
7. Have had a cerebral vascular accident in the three months prior to enrolment
8. Have had major ocular surgery in the three months prior to enrolment
9. Have had major abdominal, chest or brain surgery in the three months prior to enrolment
10. Have a known cerebral, aortic or abdominal aneurysm
11. Be breast feeding or pregnant, or plan to become pregnant while in the study
12. Be using an unreliable form of contraception (female subjects at risk of pregnancy only)
13. Be participating in another investigative drug study, parallel to, or within 4 weeks of visit 0
14. Have a known allergy to mannitol
15. Be using beta blockers
16. Have uncontrolled hypertension –e.g. for adults: systolic BP > 190 and / or diastolic BP > 100
17. Have a condition or be in a situation which in the Investigator's opinion may put the subject at significant risk, may confound results or may interfere significantly with the patient's participation in the study
18. Be 'MTT positive or incomplete'. (As evaluated in section 3.3.8.5)

* Subjects may be eligible providing a 4 week washout period occurs between cessation of hypertonic saline at visit 0 and visit 1.

4.3 Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (Appendix 1), each subject has the right to withdraw from the study at any time. An Investigator also has the right to withdraw subjects from the study in the event of intercurrent illness, AEs or other reasons concerning the health or well being of the subject. The Investigator also has the right to withdraw subjects in the case of lack of compliance or poor visit attendance.

Should a subject decide to withdraw after administration of study drug(s), or should the Investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. All subjects who are withdrawn from the study will undergo a termination visit (see below). A complete final evaluation at the time of the subject's withdrawal should be made and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason and date of withdrawal must be noted on the eCRF. If the reason for withdrawal is an AE or an abnormal laboratory test result, monitoring will continue until resolution or until an appropriate medical judgment concerning the cause or importance has been made. The specific event or test result(s) must be recorded on the eCRF.

Specific events that arise during the study that warrant withdrawal are:

- Pregnancy
- Cepacia syndrome
- Cor Pulmonale
- Pancreatitis
- Pneumothorax or hemothorax requiring the insertion of a chest tube
- Admission to intensive care
- Organ transplant
- Major abdominal, thoracic or neurosurgery
- A reduction in $FEV_1 \geq 20\%$ immediately following inhaled mannitol that persists for > 30 minutes (see section 7.1.1) *
- A reduction in $FEV_1 \geq 50\%$ immediately following inhaled mannitol
- O_2 desaturation to <89% immediately following inhaled mannitol

Termination Visit

For any subject who is withdrawn before completing all study visits, the Investigator should:

- Perform a termination visit, including all assessments scheduled for visit 4. These assessments will be performed no later than 14 days after withdrawal/discontinuation.
- Complete all appropriate CRF pages, providing the date of an explanation for the subject's withdrawal/discontinuation.
- When indicated, arrange for appropriate follow-up and / or alternative medical care of the discontinued subject.

If the subject fails to attend for a scheduled termination visit, there will be at least two attempts to contact the subject via telephone and two written communications. If these receive no reply the subject will be considered lost to follow-up.

5 TREATMENT OF SUBJECTS

5.1 Formulation and Manufacture

Mannitol powder for inhalation is manufactured by Pharmaxis Ltd, Frenchs Forest, Australia under the provisions of current Good Manufacturing Practice (cGMP). Details of formulation and manufacture are presented in the Investigator's Brochure.

5. 2 Labeling and Packaging

Investigational product is labeled according to nationally applicable regulatory requirements. Product is encapsulated prior to blister packing in aluminum foil. Blisters are contained within cartons with a dry powder inhaler device(s) and instructions for use. Product blinding is maintained via appropriate yet traceable labeling.

5. 3 Treatment Storage and Accountability

Investigational product is to be stored at room temperature (59º - 77º F or 15º – 25º C) in a secure area with restricted access. The site pharmacist is responsible for storage and maintaining accurate accountability records prior to dispensing and on return of unused treatments. The pharmacist will provide the monitor with access to the investigational product and records for periodic review. Once dispensed to subjects, investigational product should be stored at room temperature and away from humid environments such as bathrooms. Used and unused blisters will be returned to the pharmacy for reconciliation and ultimate destruction in accordance with the Sponsors requirements. Copies of the accountability records will be provided to the pharmacy monitor for inclusion in the trial master file after data base lock.

It is forbidden to use investigational product for purposes other than defined in this protocol.

5.4 Concomitant Medications

Any treatment (not explicitly excluded below) which is considered necessary for the subject's welfare may be given at the discretion of the Investigator. Medication use, current, and in the preceding 3 months will be noted. Generic names are to be used where possible, though trade names may be used for combination drugs. Start and stop dates, total daily dose, route and indication for use should be recorded. "Alternative or homeopathic therapies" are not to be recorded in the CRF.

Hypertonic saline (HS) should not be used during the study. Those using HS at screening, and wishing to take part in the study, must have a 4 week washout period between visit 0 and visit 1.

Beta blockers may interfere with $ß_2$ agonists and are therefore contraindicated during this study. Alternative medications to beta blockers to treat hypertension should be considered by the treating physician.

5. 5 Medication Withholding Periods

Prior to each study visit, medications in Table 4 below should be withheld for certain time periods as listed.

In addition, the last dose of mannitol/control and associated physiotherapy should be taken approximately 6 -12 hours prior to study visit. This will ensure that the subject is near to the trough in dose response and acute medication effects have worn off. So accurate measures of trough spirometry can be made, the treatment routine on visit days is imperative, therefore administration of respiratory medications and physiotherapy should be identical on these days and the time of day for the visit should be as close as practical.

Table 4. Medications to Be Withheld Prior To Study Days

Medication	Minimum time interval from last dose until spirometry
Mannitol/control	6 to 12 hours
Short acting bronchodilators (isoproterenol, isoetharine, metaproterenol, albuterol, levalbuterol, terbutaline) (e.g. Proventil® or Ventolin®)	6 hours
Inhaled anticholinergics or combination products (e.g. Atrovent® or Combivent®)	12 hours
Long acting β agonists e.g. salmeterol; efomoterol(e.g. Serevent® or Foradil®)	12 hours
Medium acting bronchodilators e.g. Ipratropium	12 hours
Oral bronchodilators e.g. Theophylline abd β-agonist tablets	12 hours
ICS LABA combinations e.g. fluticasone and salmeterol, budesonide and efomoterol(e.g. Advair®)	12 hours

All subjects who are subsequently discontinued or withdraw from the study should be offered alternative treatment if applicable. Treatment should be given according to normal clinical practice, after a termination visit (see Section 4.3.).

5.6 Concurrent rhDNase Use

Subjects that are using rhDNase routinely prior to enrolment in this clinical trial should continue to use rhDNase throughout the trial. Wherever possible rhDNase treatment should be kept consistent throughout the study period. If rhDNase is commenced or ceased, or the treatment schedule is changed during the study, this should be noted in the concomitant medications. A record that reflects **actual** rhDNase use, rather than prescribed use, should be maintained.

5.7 Pre-Medication Bronchodilator

All subjects are required to take a short acting bronchodilator 5 – 15 minutes prior to inhalation of the study medication. Subjects should use the same bronchodilator and dose that was administered prior to the MTT procedure. Additional bronchodilator may be used in the event of wheeze, dyspnea and chest tightness. Such use should be recorded.

5.8 Study Medication

Mannitol/control: To be administered as either 400 mg inhaled mannitol or control BID. In the blinded phase, eligible subjects are randomized in a 3: 2 ratio (active to control), while in the open label phase, all subjects will receive 400mg inhaled mannitol BID, as illustrated below:

Ratio	Blinded Phase	Duration	Open Label Phase	Duration
3	Mannitol 10 caps BID	26 weeks	Mannitol 10 caps BID	26 weeks
2	Control 10 caps BID	26 weeks		

Capsules are administered using a dry powder inhaler device (Osmohaler HR). Refer to IB for device details.

5.9 Order of Daily Procedures during the Study

The recommended order of treatment procedures is:

1. short acting bronchodilator
2. mannitol/control
3. physiotherapy / exercise*
4. rhDNase
5. inhaled antibiotics
6. inhaled cortico-steroids

The procedures 4, 5 and 6 may not be applicable to all subjects and the order of procedures 3, 4, 5 and 6 listed above is a suggestion only. Short acting bronchodilator must always precede mannitol/control.

*When possible, individual physiotherapy and exercise (if used as a substitute to physiotherapy) techniques and routines should be kept consistent throughout the study.

5.10 Rescue Medications

If a subject develops chest tightness or shortness of breath as a consequence of withholding bronchodilators or other respiratory medications on the morning of the study visits, they should take a short acting bronchodilator and phone the clinic to reschedule the visit for as soon as possible, ensuring that study schedules are maintained. All subjects will be issued bronchodilator for the duration of the study.

5.11 Unblinding Procedures

The study pharmacist will hold the IVRS unblinding activation codes. Activation of the code should be done following consultation with Pharmaxis and only for a serious adverse event or emergency where the event or emergency is considered to be study drug related. All efforts should be made to contact Pharmaxis before any randomization code is broken.

5.12 Treatment Compliance

Subjects are asked to retain all empty blister packaging and unused study medication, and return these to site at each visit. Site staff will count and record the number of returned capsules. To determine compliance, this figure will be reconciled with the number of issued capsules taking into account the number of days since dispensing. Returned study medication and packaging is to be held by pharmacy until the monitor has reconciled the returns, and approval for destruction is given. In the event of a subject withdrawal, unused medication should be returned for compliance checks.

6 ASSESSMENT OF EFFICACY AND COST EFFECTIVENESS

6.1 Primary Endpoint:

- Change in absolute FEV_1

6.2 Secondary Endpoints:

- Change in absolute FEV_1(rhDNase group)
- Pulmonary exacerbations in those taking rhDNase as a sub-group and in the total cohort
- Quality of life scores using Cystic Fibrosis Questionnaire-R
- Rescue antibiotic use (number of agents, course and days of use)
- Change in absolute FVC, FEF_{25-75} from baseline
- Days in hospital due to pulmonary exacerbations

6.3 Cost Effectiveness

Assessment of Cost-Effectiveness:

- Total costs incurred in intervention and control groups
    * Costs associated with inhaled mannitol
    * Cost of antibiotic use and rescue medication
    * Costs of hospitalizations and other secondary care services used
    * Cost of primary and community care services used
- Indicators of effectiveness and quality of life for intervention and control groups
    * As above
- Determination of cost-effectiveness ratios
- Sensitivity analysis
    * To assess extent to which variation in parameter estimates affect cost effectiveness ratios

7 ASSESSMENT OF SAFETY

7.1 Secondary Endpoints

- Laboratory tests: complete blood count, BUN, liver function tests (AST, ALT, total bilirubin, Alkaline phospatase, GGT and indirect bilirubin), electrolytes and blood urea nitrogen.
- Adverse events
- Sputum microbiology (qualitative)
- Quantitative sputum microbiology (Log_{10} value for the sum of S. *aureus* and P. *aeruginosa* expressed as colony forming units per gram of sputum)
- Physical examination findings

7.2 Adverse Events

7.2.1 Procedures for Adverse Events and Intercurrent Illnesses

The appropriate clinical staff at the study site will handle any study related medical emergencies involving trial subjects.

For purposes of collecting and evaluating all information about Pharmaxis drugs used in clinical trials, a clinical trial AE is any unfavorable or unintended change in the structure, function or chemistry of the body, temporally associated with the use of a Pharmaxis product, whether or not considered to be related to the product. Any worsening (e.g. clinically significant adverse change in frequency and/or intensity) of a pre-existing condition, which is temporally associated with the use of a Pharmaxis product, is also an AE.

Changes resulting from normal growth and development, which do not vary significantly in frequency or severity from expected levels, are not to be considered AEs. Examples of this may include, but are not limited to: teething, period pain, typical crying in infants and children, bedwetting, the onset of menses or menopause occurring at a physiologically appropriate time.

Planned hospital admissions for pre-existing conditions are not considered to be adverse events.

Bronchoconstriction is an expected effect during the MTT procedure and is not to be considered an adverse event unless the bronchoconstriction causes a $\geq$50% fall in FEV_1 or the subject desaturates to $\leq$89%

If at any other time during or immediately following the administration of the mannitol/control powder, the subject experiences a fall in FEV_1 of $\geq$20% due to bronchoconstriction, the subject should be monitored for 30 minutes before having the FEV_1 measurement repeated. Subjects who have not recovered their FEV_1 to <20%, at this point and provisos 1 and 2 (below) have been met, should not receive further study medication.

1) a suitable bronchodilator was taken prior to administration of the mannitol/control;

2) the investigator determines that the fall in FEV_1 is bronchoconstriction and not due to mucus plug or floppy airway collapse. This can be tested by administering positive pressure via a PEP

mask or Acapella device or similar and repeating the FEV_1 maneuver.

If the fall in FEV_1 persists below 20% at 30 minutes post mannitol/control, subjects should discontinue study medication but should be encouraged to continue in the study and undergo all study procedures (that do not require administration of mannitol/control) as scheduled up until the end of visit 4 when the base study is deemed to be complete.

7.2.2 Adverse Events Recording Requirements

Baseline Evaluation

At screening, the Investigator will record any current medical illnesses and any medications used by the subject to treat such conditions. Recurring symptoms associated with pre-existing conditions will not be considered AEs during the study, unless they have a *clinically significant increase in severity and/or frequency*. Clinically significant out of range laboratory results at screening will be recorded as pre-existing conditions. If a pre-existing condition is discovered during the study, but not recorded at screening, a correction to the study record should be made.

Prior to enrolment, study site personnel will evaluate and record the subject's medical condition(s). During the study, site personnel will evaluate and record any change in the condition(s) and/or the occurrence of any AEs.

Study Periods Evaluation

Subjects and/or parents/caregivers (if appropriate) will be questioned for the occurrence of any new or worsening signs or symptoms at each visit by the following methods:

* Information volunteered by the subject
* Open ended and non-leading questions such as: Have you had any health problems since your last visit?
* Observation by the investigational team, other care providers or relatives
* Study Diary review

The Investigator will determine whether the signs and symptoms represent clinically significant changes from the subject's baseline condition, and if so, should be recorded as an AE.

- All AEs will be followed until resolution or until an appropriate medical judgment concerning the cause or importance has been made.
- Adverse Events will be captured from screening visit until 12 hours following the last study visit.
- Subjects, who are withdrawn because of a positive or incomplete MTT, will be followed for adverse events for a period of 48 hours.
- Subjects who withdraw from the study, but who receive study medication will be followed for adverse events for a period of 7 days post last dose of medication.
- AEs may also occur in screened subjects during any pre allocation baseline period as a result of a protocol-specified intervention including washout or discontinuation of usual therapy or a procedure. Such AEs will be captured.

The Investigator will evaluate all AEs as to:

- Seriousness: See Serious Adverse Events section
- Severity

    * Mild *(awareness of sign or symptom but easily tolerated)*
    * Moderate *(discomfort causes interference with usual activity)*
    * Severe *(incapacitating, or unable to do usual activities)*

- Duration: Record the onset and stop dates of the event. If less than one day, record the appropriate length of time and units

- Action taken: Did the event cause the study drug or procedures to be discontinued or postponed?

- Relationship to study drug: Did the study drug cause the AE? The likelihood that the study drug caused the AE must be determined by the Investigator. The following criteria should be used to assist the Investigator to determine causality between the AE and the study drug

Exposure:

- Is there evidence to show that the subject was exposed to the drug such as reliable history, acceptable compliance assessment (pill count, etc.), expected pharmacological effect, or measurement of drug/metabolite in bodily specimen?

Time Course:

- Was there a reasonable time sequence between exposure and AE?
- Is the time of onset of AE compatible with a drug induced effect?

Likely Cause:

- Can the AE be reasonably explained by other etiology such as underlying disease, other drug(s), or other host environmental factors?

Dechallenge:

- Was the dose of test drug discontinued or reduced?
- If yes, did the AE resolve or improve?
    * If yes, this is a positive dechallenge
    * If no, this is a negative dechallenge

    Note: This criterion is not applicable if:
        - the AE resulted in death or permanent disability
        - the AE resolved/improved despite continuation of the test drug
        - the study is a single dose study

Rechallenge:

- Was the subject re-exposed to the test drug in this study?
- If yes, did the AE recur or worsen?
    * If yes, this is a positive rechallenge
    * If no, this is a negative rechallenge

    Note: This criterion is not applicable if:
        - the AE resulted in death or permanent disability
        - the study is a single dose study

If a rechallenge is planned for an AE which was serious and which may have been caused by the study drug, or if re-exposure to the study drug poses additional potential significant risk to the subject, then the

rechallenge must be approved in advance by the medical monitor and the local institutional ethics committee.

Consistency with study drug profile:

- Is the clinical presentation/pathology consistent with previous knowledge regarding the study drug or drug class pharmacology or toxicology?

The assessment of relationship will be reported by the Investigator according to his/her best judgment, including consideration of the above elements. Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a drug relationship):

***Definitely related** to study drug*:

- There is evidence of exposure to the study drug
- The temporal sequence of the AE onset relative to administration of the test drug is reasonable
- The AE is more likely explained by the test drug than by another cause
- Dechallenge is positive
- Rechallenge (if feasible) is positive
- The AE shows a pattern consistent with previous knowledge of the test drug or test drug class

***Probably related** to study drug*:

- There is evidence of exposure to the study drug
- The temporal sequence of the AE onset relative to administration of the test drug is reasonable
- The AE is more likely explained by the test drug rather than by another cause
- Dechallenge (if performed) is positive
- Rechallenge (if performed) is positive or ambiguous

***Possibly related** to study drug*:

- There is evidence of exposure to the study drug
- The temporal sequence of the AE onset relative to administration of the test drug is reasonable
- The AE could have been due to another equally likely cause
- Dechallenge (if performed) is negative or ambiguous
- Rechallenge (if performed) is negative or ambiguous

***Probably not related** to study drug*:

- There is evidence of exposure to the study drug
- There is another more likely cause of the AE.
- Dechallenge (if performed) is negative or ambiguous
- Rechallenge (if performed) is negative or ambiguous

***Definitely not related** to study drug*:

- The subject did not receive the study drug OR
- Temporal sequence of the AE onset relative to administration of the study drug is not reasonable OR
- There is another obvious cause of the AE
- Dechallenge (if performed) is negative
- Rechallenge (if performed) is negative

An AE that later meets the criteria for a serious adverse event (SAE) within the study period must be reported as a serious adverse event. After the study period, only if a serious adverse event is believed to be related to the study drug administration should it be reported.

7.3 Serious Adverse Events

A serious adverse event for this study is defined as any unfavorable medical occurrence that:

1. **Results in the death of the participant**

…….

2. **Is life-threatening**

(*Note: the term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe*)

Examples: Pacemaker failure; gastrointestinal hemorrhage; bone marrow suppression; infusion pump failure, which permits uncontrolled free flow resulting in excessive drug dosing

……
…

3. **Requires inpatient hospitalization or prolongation of existing hospitalization**

(*Note: hospitalization is defined as inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation) (Note: Hospitalization for a pre-existing condition which has not worsened, including/or hospitalization for an elective procedure, <u>does not</u> constitute a serious adverse event*).

Examples: Anaphylaxis; pseudomembranous colitis; or bleeding causing or prolonging hospitalization

……
…

4. **Results in persistent or significant disability or incapacity**

Examples: Cerebrovascular accident due to drug induced hypercoagulability; toxicity; peripheral neuropathy

……
…

5. **Is a congenital anomaly or birth defect**

Examples: Vaginal cancer in female offspring from diethylstilbestrol during pregnancy; malformation in the offspring caused by thalidomide

……
…

6. **Is an important medical event**

(*Any event which is not immediately life-threatening and does not result in death or hospitalization but which may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed above*)

Examples: Acetaminophen overdose induced hepatotoxicity requiring treatment with acetylcysteine to prevent permanent damage; burns from radiation equipment requiring drug therapy; breakage of a screw requiring replacement of hardware to prevent malunion of a fractured long bone.

……
…

Immediately upon notification of the occurrence of any serious adverse event, the Principal Investigator

or designee must contact the Clinical Research Associate, Pharmacovigilance Project Manager (PPM) or Medical Director (see contact list) at Pharmaxis by fax +61 (0)2 9454 7255.

Serious adverse events must be reported to Pharmaxis within 24 hours of notification of the occurrence.

The site will complete the Serious Adverse Event Form with as much detail as possible. The site will fax this form to the study CRA or PPM. All AEs must be reported in the case report form.

The Investigator is responsible for an assessment of causality, intensity, and relationship to study treatment. Actions taken and outcomes must also be recorded. All AEs and SAEs will be followed until an appropriate medical judgment concerning the cause or importance has been made, or the event is resolved.

The Sponsor is responsible for reporting adverse events to the relevant governing authorities in the time frames and methodology applicable according to international and local law.

7.4 Data Safety Monitoring Board

This data safety component of this study will be conducted by the Cystic Fibrosis Foundation Data Safety Monitoring Board whose offices are located in Tucson, Arizona, USA. The primary responsibility of the DSMB is to protect the safety and welfare of patients participating in this clinical trial and to ensure the integrity of the study. The DSMB will comprise of a Data Monitoring Committee (DMC) which will review clinical data relating to safety and efficacy and ensure the continued scientific validity and merit of the study.

DSMB duties:

- Reviewing significant adverse events and adverse event trends
- Examining accumulated outcome and safety data in order to make recommendations concerning continuation, termination or modification of the trial based on the effects of the interventions under study
- Reviewing major study design modifications proposed by the sponsor prior to implementation
- Reviewing the general progress of the studies with regard to accrual, protocol violations, and study conduct

The DSMB will receive SAEs promptly, as well as periodic safety reports, therefore facilitating a timely response to potential safety issues. The DSMB will also receive one report for the purposes of an interim analysis. The web based data capture system is programmed to produce regular reports of study progress and conduct and other requirements as deemed necessary.

8 STATISTICS

8.1 Objectives

Primary objective

- To determine whether inhaled mannitol compared to control improves FEV_1 in patients with CF

Secondary Objectives

- To determine whether inhaled mannitol compared to control improves FEV_1 in patients with CF on existing RhDNase treatment

And to assess whether inhaled mannitol treatment:

- Reduces pulmonary exacerbations in those taking RhDNase as a sub-group and in the total cohort
- Improves quality of life
- Reduces days on IV antibiotics, rescue oral or inhaled antibiotics
- Reduces days in hospital due to pulmonary exacerbations
- Improves other measures of lung function
- Demonstrates an appropriate safety profile (adverse events, hematology, biochemistry, sputum microbiology ((both qualitative and quantitative)), physical examination)
- Reduces hospital and community care costs

8.2 Efficacy, Safety and Health Economic Outcome Measures

8.2.1 Efficacy Measures

Primary Outcome Measures

- Change in absolute FEV_1

Descriptive analysis will show the change from baseline in FEV_1. Descriptive statistics will include the mean change, the standard deviation, the median change, the minimum change and the maximum change, at each of the post baseline FEV_1 assessments (weeks 6, 14 and 26).

Inferential analysis will involve a repeated measures analysis of the change in FEV_1 from baseline, taking age and baseline FEV_1 as covariates for each patient. Inhaled mannitol dose will be categorized at two levels in order to assess dose response: Control and 400mg. The model will take the form:

*change in FEV_1 from baseline = dose + week + dose*week + age + baseline FEV_1.*

Patient number will also be specified as a random effect in the model. The treatment effect of 400mg of inhaled mannitol will be estimated by the value of the dose coefficient from the model. The interaction of dose and time (Study Week) will also be reported in order to examine changes in effect over the course of the initial 26 week study period. Least squares mean values and standard errors for the change from baseline in FEV_1 at each post-baseline assessment, by dose level, will be presented in tables and

also as a graph. More comprehensive analysis details will be provided in the final study SAP prior to analysis.

Secondary Outcome Measures

- Change in absolute FEV_1 (rhDNase group)

The descriptive analysis will be the same as described for the primary efficacy outcome measure.

- Pulmonary exacerbations (as defined)

The number and percentage of patients experiencing at least one pulmonary exacerbation event in the initial 26 week study period will be presented by dose level (control and 400mg).

Pulmonary exacerbation rates for each dose level in the first 26 week study period will be compared using Poisson regression analysis. Age and baseline disease severity (% predicted FEV_1) will be used as covariates for each patient. The model will take the following form:

number of exacerbation events = dose + age + baseline FEV_1*.*

The number of days on Study in the initial 26 week period will be included in the model as an offset, thereby adjusting for differing lengths of exposure on study for different patients. Rates will be expressed as the number of events per person year of observation. 95% confidence intervals for the rates will be shown. The rate ratios comparing inhaled mannitol 400mg to the control will be presented. 95% confidence intervals for the rate ratio will be shown. This analysis will be undertaken on the safety population. The analysis will also be repeated for exacerbations in the open label period.

- Quality of Life Scores using Cystic Fibrosis Questionnaire-R (Quittner)

Component questions in the questionnaire will be appropriately transformed so that the best response is uniformly the highest score, and the worst response is uniformly the lowest score. The total will be the sum of the component question responses. At each visit, descriptive statistics (mean, standard deviation, median, minimum and maximum scores) will be presented by dose level (control and 400mg). Also, at weeks 14, and 26, change from baseline scores will be presented using the same descriptive statistics.

Inferential analysis will involve a repeated measures analysis of the change in CFQ-R domain from baseline, taking age, disease severity at baseline, and baseline value as covariates for each patient. Inhaled mannitol dose will be categorized at two levels in order to assess dose response: Control and 400mg. The model will take the form:

*change in CFQ-R domain from baseline = dose + week + dose*week + age + baseline FEV1 + baseline CFQ-R domain.*

Patient number will also be specified as a random effect in the model. The treatment effect of 400mg of mannitol will be estimated by the value of the dose coefficient from the model. The interaction of dose and time (Study Week) will also be reported in order to examine changes in effect over the course of the initial 26 week study period. Least squares mean values and standard errors for the change from baseline in CFQ-R domain at each post-baseline assessment, by dose level, will be presented in tables and also as a graph.

- Rescue antibiotic use (number of agents, course and days of use)

Rescue antibiotics used during the first 26 weeks of treatment will be displayed individually for each patient. Additionally, a summary tabulation of rescue agent showing the number of uses will be shown

by dose level (control and 400mg). The number and percentage of patients with no rescue antibiotic use, and 1, 2, 3 and >3 distinct episodes of rescue antibiotic use will also be shown. The average number of days of use of rescue antibiotics will also be tabulated by dose level (for both the safety population, and the subset of the safety population that required at least one rescue antibiotic in the first 26 week period). The standard deviation, median, minimum and maximum number of days of rescue antibiotic use will also be shown. Exposure to rescue antibiotics will also be estimated. Exposure to rescue antibiotics will be expressed as the number of day's use of rescue antibiotics per person year of observation. Data will be analyzed using Poisson regression as described for pulmonary exacerbations. If the data for rescue antibiotic use displays evidence of over dispersion in the Poisson regression analysis, a similar model using the negative binomial distribution will be used to analyze the data.

This analysis will be undertaken on the safety population. The analysis will also be repeated for rescue antibiotic use in the open label phase.

- Change in FVC, FEF_{25-75} from baseline

These data will be analyzed using similar techniques to those described for the primary efficacy outcome measure. Analysis will be undertaken on both the ITT and PP populations.

- Days in hospital due to pulmonary exacerbations

Days in hospital due to pulmonary exacerbations during the first 26 weeks of treatment will be displayed individually for each patient. The number and percentage of patients with no days in hospital, and 1, 2, 3 and >3 days in hospital (across all hospitalization events) will also be shown by dose level (control and 400mg). The average number of days in hospital will also be tabulated by dose level (for both the safety population, and the subset of the safety population that required at least one day in hospital due to pulmonary exacerbations in the first 26 week period). The standard deviation, median, minimum and maximum number of days in hospital will also be shown.

The rate of hospitalization due to pulmonary exacerbations in the first 26 week study period will also be estimated. Hospitalization rates will be expressed as the number of days of hospitalization per person year of observation. Data will be analyzed using Poisson regression as described for pulmonary exacerbations. If the data for days in hospital displays evidence of over dispersion in the Poisson regression analysis, a similar model using the negative binomial distribution will be used to analyze the data.

This analysis will be undertaken on the safety population. The analysis will also be repeated for days in hospital due to pulmonary exacerbations in the open label phase.

8.2.2 Measures of Safety

- adverse events

The number and percentage of patients experiencing adverse events will be tabulated. Additional summary data will be presented for:

- serious adverse events,
- treatment related adverse events (defined as being possibly, probably or definitely related to treatment in the opinion of the investigator),
- treatment related serious adverse events,
- adverse events leading to study withdrawal,
- treatment related adverse events leading to study withdrawal, and
- deaths

In addition, adverse events will be summarized by MedDRA system organ class and preferred term. Each of these analyses will be conducted at the patient level, that is, multiple adverse events within the same MedDRA system organ class and preferred term for a particular patient will only be counted once and the denominator for the percentage calculation will be the number of patients in the safety population.

All adverse event summary tables will be presented by dose level (control and 400mg mannitol).

- qualitative sputum microbiology: changes from baseline,
- quantitative sputum microbiology: change in number of colony forming units for s. *aureus* and p. *aeruginosa* morphotypes per gram of sputum expressed as $Log_{10,}$
- physical examination: changes from baseline,
- blood tests: changes from baseline for complete blood count, electrolytes, BUN and LFT

8.2.3 Health Economic Measures

- Cost effectiveness including total costs of hospital and community care

A standard costing method will be used to assess the total health care cost from a community-health-service and hospital perspective. Subject's personal costs will be excluded. Included in the assessment will be: hospital admissions (inpatient, outpatient, day case); radiological investigations, blood tests, medication use, and the use of community services (e.g. visits to general practitioners, district nurses and physiotherapists). Resources will be recorded from medical records, discharge summaries and subjects' diaries.

Unit costs will be obtained from finance departments at the hospitals involved in the study and a district general hospital. Costs, both resource and unit, will include health professionals' time, consumables and overheads. Costs will be derived from documents such as USP-NF; Current Procedural Terminology from the American Medical Association; the Medicare Coverage Database or as nationally appropriate for other countries, and community care costs from published data

The Health Utility Index (HUI) value will be used to develop Quality Adjusted Life Years (QALY). The change in HUI value induced by the treatment will be multiplied by the duration of the treatment effect to provide the number of QALY's gained. QALY's will be incorporated with medical costs to arrive at a final common denominator of cost/QALY. This parameter will be used to compare the cost-effectiveness of mannitol with control.

Sensitivity analysis using cost and resource use data and effects and QOL data will also be undertaken.

8.3. Justification of Sample Size

8.3.1 Two Arm Study Design

The primary objective of the study is to show an effect of mannitol compared with control on absolute FEV_1 in CF patients.

Sample size was estimated based on demonstrating an improvement in FEV_1 of mannitol in all patients (primary objective); in RhDNase + patients (secondary objective) and a change in exacerbation rates across all patients (secondary objective).

With 80 patients per arm, there is 96% power to detect both a difference of 120mL in change from baseline of FEV_1 between the control group and the 400mg BID mannitol group and 80% power to detect a difference in rates of pulmonary exacerbations over the course of a 26 week study, assuming pulmonary exacerbation rates of 0.42 events per patient-year in patients treated with dry powder mannitol, and 0.96 event per patient-year in patients in the control group.

A total of 300 patients will be randomized in a ratio of 3:2 (mannitol: control). This assumes a screen failure/drop out rate of 30% in each arm. It is estimated that approximately 65% of subjects randomized will be using RhDNase. Additional subjects may need to be recruited if screen failure/drop out rates differs to the assumptions made, or other factors of attrition exceed predictions.

Details and further discussion of the sample size estimation used are shown in Appendix 7.

8.3.2 Multiple Statistical Comparisons

No adjustments have been made to the power or sample size estimates for multiple statistical comparisons. Power was estimated in section 8.3.1 to be approximately 80% with 45 patients per group, and approximately 96% with 80 patients per group. The primary analyses are described in section 8.5. Analysis from the intent to treat (ITT) population (defined in section 8.4.2) will take precedence over analysis from the per protocol (PP) population (defined in section 8.4.3).

8.4 Study Population

8.4.1 Sample Population

Cystic fibrosis, aged $\geq$ 6 years, baseline FEV_1 $\geq$40% and <90% predicted using NHanes III or Wang for children < 8 years, tables, either gender, not be pregnant or breast feeding, no intolerance to mannitol or $beta_2$ agonists, not participating concurrently or within the previous 4 weeks in another investigative drug study. No concurrent use of hypertonic saline or beta blockers.

8.4.2 Intent to Treat Population (ITT)

All subjects who are randomized and have received at least one dose of study medication.

8.4.3 Per Protocol Population (PP)

The PP population includes all subjects with no major protocol violations who have demonstrated $\geq$ 80%compliance with the intervention.

8.4.4 Statistical Criteria for Study Termination

The study will be terminated once the required numbers of subjects to meet statistical analysis requirements above have been enrolled.

8.5 Data Analysis Considerations

Results will be summarized overall using univariate statistics including means, standard deviations, ranges (including missing responses), medians and proportions (including cross tabulations), as appropriate to the data. Where necessary, log normalization will be undertaken to produce geometric means, and for use in subsequent statistical tests.

AE's will be classified according to the MedDRA dictionary and will be presented by counting the number of subjects reporting each event by treatment. The number and percentage of subjects reporting treatment emergent adverse events will be tabulated by system organ class and preferred term. AE's will also be summarized by both severity and relationship to study drug.

Safety data collected will be analyzed using descriptive statistics - means, proportions and confidence intervals, documenting the number, severity and type of adverse events, and changes from baseline to follow up in vital signs. Where appropriate, F tests and χ^2 tests will be performed to determine significant before/after changes, and differences between the study groups. The safety analysis will be performed on the ITT/PP populations.

The incidence of laboratory results outside the normal range will be summarized by treatment group and time point. Laboratory results outside the range of normal and considered to be clinically significant will be listed for clinical review.

The primary and key secondary analyses will use generalized linear models to compare the study groups in regards to FEV_1. Adjustments in the models will be made for age and sex, and disease severity Treatment group will be included in the model as a categorical variable. Should the overall model fit be significant at the 5% level, orthogonal contrasts will be performed using the baseline (pre-intervention) level as the reference to examine changes over time in the outcome. The models will be analyzed using SAS V9.1. The findings will include the slope, standard error, and significance tests of the model and study protocol indicator.

8.5.1 Handling of Dropouts and Missing Data

The primary endpoint will be estimated using ITT and PP populations (results from the ITT analysis will take precedence over findings from the PP analysis). All other measures will be performed using the ITT population and where applicable also the PP population. Where a subject has missing data on a continuous outcome measure, the baseline score will be used. This replacement is appropriate since it is expected that scores will improve from or remain similar to baseline, rarely getting worse.

The pattern of missing data for the primary endpoint variable will be summarized descriptively. If there is evidence of differential distribution of missing data between groups, consideration will be given to conducting a secondary efficacy analysis based on the primary efficacy analysis, using an alternative data imputation method (to be defined in the statistical analysis plan of this study).

8.5.2 Interim Analysis

The data safety monitoring board will examine accumulated outcome and safety data in order to make recommendations concerning continuation, termination or modification of the trial based on the effects of the interventions under study. An interim analysis is planned for midway through the study and a type I error rate of 5% will be maintained by using the Peta-Haybittle rule. This means a significance level of 0.001 will be used for testing the efficacy endpoint at the interim analysis and a significance level of 0.0498 will be used for testing the primary efficacy endpoint at the end of the study. No adjustment will be made to the significance level for multiple statistical comparisons conducted as part of the secondary analyses.

A safety and efficacy analysis will be conducted at completion of the initial 26 week study for all subjects. A safety analysis will be conducted following the completion of the 26 week open label phase.

8.5.3 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be written and finalized prior to any lock of the study database. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol. Additional analyses may be added. Tables, listing and figures shells will also be provided.

9 ETHICS

9.1 Informed Consent

This study will be conducted in full accordance with the current revision of the Declaration of Helsinki and the *Good Clinical Practice: Consolidated Guideline* approved by the International Conference on Harmonization (ICH).

This study will be conducted in compliance with 21 CFR Part 50 for informed consent. Written informed consent will be obtained from each subject before any procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

The subject's willingness to participate in the study will be documented in writing in a consent form, which will be signed by the subject with the date and time of that signature indicated. The Investigator(s) will keep the original consent forms and copies will be given to the subjects.

Written and/or oral information about the study in a language understandable by the subject will be given to all subjects. The information provided must include an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force.

9.2 Health Authorities and Institutional Review Boards

The Investigator(s) will ensure that the conduct of the study conforms to 21 CFR Part 56, the Declaration of Helsinki (current revision) and with national laws and regulations for clinical research.

Before starting this study, the protocol will be submitted to the national/local health authorities and to the IEC/IRB for evaluation. As required, the study will not start before the IEC/IRB and health authorities give approval in writing and this approval is dated before enrolment of the first subject. Any amendments to the protocol, other than administrative amendments, will be first approved by the Sponsor and then submitted to the IRB and health authorites. The IEC/IRB and health authorities will also be notified of SAE's in the nationally appropriate format and of the completion or termination of the study.

9.3 Confidentiality Regarding Study Subjects

All information obtained during the conduct of the study with respect to the subject's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing.

The Investigator must ensure that each subject's anonymity is maintained. On CRF's and other documents submitted to the Sponsor or its authorized representatives, subjects must not be identified by name. Instead, subjects will only be known by a unique study number allocated to them in order to ensure confidentiality on all study documentation. The study number will include a site identifier. A unique study number will be allocated at both enrolment and randomization. Study numbers will be allocated to subjects after they have signed the informed consent form and they have been judged to meet the study eligibility requirements. Subjects will retain this unique number throughout the study. The Investigator will keep a separate log of these codes.

In order to comply with government regulatory guidelines and to ensure subject safety, it may be necessary for the Sponsor and its representative, the CRO personnel, the local research review board, or a government regulatory authority to review subjects' medical records as they relate to this study.

Documents that are not for submission to the Sponsor or the CRO (e.g., consent forms) will be maintained by the Investigator in strict confidence, except to the extent necessary to allow monitoring by the Sponsor and the CRO, and auditing by regulatory authorities. No documents identifying subjects by name will leave the investigative site and subject identity will remain confidential in all publications related to the study.

10 QUALITY ASSURANCE & MONITORING

10.1 Protocol Amendments

Any change to the protocol must be handled as a protocol amendment. Any potential amendment must be approved by the Sponsor. All substantial amendments to the protocol must be submitted as appropriate to the concerned regulatory authorities and the IEC.

The Investigator must await written IEC/IRB and regulatory approval of substantial protocol amendments before implementing the changes, except where the changes are necessary to eliminate apparent immediate hazard to subjects. In these cases, the measures can be implemented immediately but the IEC/IRB and concerned regulatory authorities must be notified as soon as possible of the new events, the measures taken, and the plan for further action. Administrative amendments which require notification but not written approval, can be implemented once the appropriate concerned regulatory authorities and the IEC/IRB have confirmed receipt of the notification.

If, in the judgment of the local IEC/IRB, the Investigator and/or Sponsor, the protocol amendment alters the study design, procedures and/or increases the potential risk to the subject, the currently approved written informed consent form will require modification. The modified informed consent form must also be reviewed and approved by the Sponsor, appropriate regulatory authorities, and the IEC/IRB. In such cases, repeat informed consent must be obtained from subjects enrolled in the study before participation continues.

10.2 Protocol Violations and Deviations

The protocol must be read thoroughly and the instructions must be followed. However, exceptions will be made in emergency situations when the protection, safety, and well-being of the subject requires immediate intervention based on the judgment of the Investigator or a responsible, appropriately trained, and credentialed professional(s) designated by the Investigator as a sub-investigator.

In the event of a significant protocol deviation due to an emergency, accident, or error, the Investigator or designee must contact the Medical Monitor at the earliest possible time by telephone. This allows for an early joint decision to be made as to whether or not the subject should continue in the study. The Investigator, the Sponsor, and the Medical Monitor will document this decision.

10.3 Information to Study Personnel

The Investigator(s) is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting the practical performance of the study and during the course of the study (e.g. when new staff become involved).

The monitor(s) is responsible for initiating the site, for ensuring site compliance with the protocol and for closing out the site at the end of the study. Additional information available during the study should be given as agreed upon, either by the Investigator(s) or the monitor (s), and always when new staff members become involved in the study.

10.4 Study Monitoring

The Sponsor has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and ICH GCP guidelines. As such, in order to fulfil these obligations and to maintain current of study progress, the Sponsor's monitors or representatives will visit the investigative sites during study conduct, in addition to maintaining telephone and written

communication. On-site visits, telephone calls, and regular inspection of the CRF's will be conducted in order to assess subject enrolment, compliance with protocol procedures, completeness and accuracy of data entered on the CRF's, verification of CRF data against original source documents, and occurrence of AEs. The Investigator must provide the monitor with full access to all source and study documents.

Sponsor assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study. The Investigator must agree to Sponsor-authorized personnel having direct access to the clinical (including the subject's medical records, whether electronic or paper based) files and clinical trial supplies (dispensing and storage areas) for all study subjects considered for study entry for the purpose of verifying entries made in the CRF, and assist with their activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator. If access to the subject's electronic medical record is prohibited by the institution, certified copies must be made available for source document verification.

The site must complete the CRF's in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Whenever a subject name is revealed on a document that is to be collected for the Sponsor the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the subject number as identification.

10.5 Audit and Inspection

The Sponsor or its representative may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of CRF's with source documents. All medical records (progress notes) must be available for audit. The Investigator agrees to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the Investigator during or after the study. The Investigator or designee should contact the Sponsor/CRO immediately if this occurs. He/she must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner.

The purpose of an audit is to assess whether ethics, regulatory and quality requirements are fulfilled.

11 SOURCE DOCUMENTS AND DATA COLLECTION

11.1 Access to Source Documents

The monitor(s), auditor(s), and regulatory inspector(s) will be given direct access to source data and documentation (e.g. medical records, laboratory reports, diagnostic imaging etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements and privacy regulations. Where medical records are electronic, access will be given to the monitor for data verification or if institutional procedures prohibit access, a certified copy of the record will be made available to the monitor for data verification.

11.2 Study Record / Progress Notes

During each study visit, a physician participating in the study will maintain progress notes, in ink, in the subject's medical records to document all significant observations. At a minimum, these notes will contain:

- The date of the visit and the corresponding day or visit in the study schedule (e.g., screening, Visit 1, Visit 2, etc.)
- General condition and status remarks by the subject, including any *significant* medical findings. The severity, frequency, duration, and resolution of any reported AE, and the Investigator's assessment as to whether or not the reported AE is study drug-related.
- Changes in concomitant medications or dosages.
- A general reference to the procedures completed.
- The signature or initials of all physicians making an entry in the medical record (progress notes).

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents will be promptly transcribed to the appropriate section of the CRF.

Changes to information in the medical record (progress notes), CRF, and other source documents will be initialled and dated on the day the change is made by the Investigator or designee. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change.

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs and recorded data from automated instruments.

All source documents from this study will be maintained by the Investigator and made available for inspection by authorized persons. The original signed informed consent form for each subject shall be filed with records kept by the Investigator and a copy shall be given to the subject.

11.3 Completing, Signing, and Archiving Case Report Forms

The Investigator(s) must keep a separate subject identification list showing code numbers, names, and dates of birth to allow unambiguous identification of each subject included in the study. A note will be made in the hospital or clinical medical records, if appropriate, that the subject is participating in a clinical study.

The site will be responsible for ensuring that a computer and internet access are available as needed for eCRF completion by study staff and for eCRF monitoring by Pharmaxis representatives.

All eCRF pages (e.g. visits) should be signed by the study coordinator. Any corrections to the data will be made in a manner that does not obscure the original entry and will be dated and initialled by the Investigator or assigned designee. An audit trail will secure all changes in the data flow over time.

It is important to have data collection in a timely manner, meaning that the Investigator/study coordinator shall complete the eCRF pages continuously and submit for monitoring. The monitor(s) and data manager(s) will request additional data and clarification of data through the eCRF page and the queries should be resolved continuously. It is important to have all queries resolved as soon as possible.

The data collection will be performed using an electronic data capture solution. Data should be entered by the site continuously during the subject visit. The monitor(s) and data manager(s) will request additional data and clarification of data through the eCRF page and the queries should be resolved continuously. When the monitor has completed the source data verification and all queries have been resolved the eCRF page will be locked.

11.4 Data Management and Data Control

The Sponsor will be responsible for the processing and quality control of the data. Data management in connection with electronic data capture technique is quite different from traditional paper CRF. Most of the data management process is carried out by the programming of eCRF pages with respect to measurement intervals and logical checks. The monitor(s) fulfils a portion of the data management function through watching over the eCRF pages and the verification through the source data verification (SDV) process.

Source data, source documents, hard copy of completed eCRFs, copies of protocols and protocol amendments, drug accountability forms, correspondence, subject identification lists, informed consent forms, and other essential documents must be retained for a period of at least 15 years or at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the Sponsor to inform the Investigator(s)/institution(s) when these documents need no longer be retained.

The original record of the eCRFs, will be archived by the Sponsor for the lifetime of the product. No study document or image should be destroyed without prior written agreement between the Sponsor and the Investigator(s). Should the Investigator(s) wish to assign the study records to another party or move them to another location, advance written notice should be given to the Sponsor.

11.5 Study Centre File Management

The Investigator is responsible for assuring that the Study Centre File is maintained. The Study Centre File will contain, but will not be limited to, the information listed below:

1. Current Investigator's Brochure and any previous versions;

2. Current, signed version of the protocol and any previous versions of the protocol;
3. Protocol amendments (if applicable);
4. Operations Manual (if applicable);
5. Current informed consent form (blank) and any previous versions of the informed consent form;
6. Curricula Vitarum of Investigator(s) and sub-investigator(s) and photocopies of their respective license(s) where required by law;
7. Documentation of IRB approval of the protocol, the informed consent form, any protocol amendments, and any informed consent form revisions;
8. All correspondence between the Investigator, IRB, and the Sponsor/CRO relating to study conduct;
9. Laboratory certification(s);
10. Monitoring logs;
11. Study drug invoices;
12. Signature list of all staff completing CRF's; and
13. Signature list of all staff completing drug accountability summaries.

12 FINANCING AND INSURANCE

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included subject, based on the calculated costs of performing the study assessments in accordance with the protocol, and the specified terms of payment will be described in the contract. The contract should describe whether costs for pharmacy, laboratory and other protocol-required services are being paid directly or indirectly. Financial Disclosure Statements will need to be completed, as requested by FDA CFR 21 part 54.

The study is covered under a clinical trials insurance policy. The certificate of insurance and an information leaflet containing essential information about the insurance coverage can be provided upon request.

13 REPORTING AND PUBLICATION OF RESULTS

A final clinical study report will be prepared according to the ICH guideline on Structure and Contents of Clinical Study Reports. A final clinical study report will be prepared regardless of whether the trial is completed or prematurely terminated. The Sponsor will provide each Investigator with a copy of the final report for retention.

Policies regarding the publication of the study results are defined in the Clinical Trial Site Agreement.

14 REFERENCES

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15 APPENDICES

15.1 Appendix 1: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964
and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989;
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996;
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the Sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for review, information regarding funding, Sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
11. The subjects must be volunteers and informed participants in the research project.
12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the subject's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the subjects who are research subjects.

2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

3. At the conclusion of the study, every subject entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the study.

4. The physician should fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study must never interfere with the subject-physician relationship.

5. In the treatment of a subject, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the subject, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

15.2 Appendix 2: Elements of Informed Consent

ELEMENTS OF INFORMED CONSENT

Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

- That the trial involves research.
- The purpose of the trial.
- The trial treatment(s) and the probability for random assignment to each treatment.
- The trial procedures to be followed including all invasive procedures.
- The subject's responsibilities.
- Those aspects of the trial that are experimental.
- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, foetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- The compensation and/or treatment available to the subject in the event of trial-related injury.
- The anticipated prorated payment, if any, to the subject for participating in the trial.
- The anticipated expenses, if any, to the subject for participating in the trial.
- That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- That the monitor(s), the auditor(s), the IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
- That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
- That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
- The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
- The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
- The expected duration of the subject's participation in the trial.
- The approximate number of subjects involved in the trial.

15.3 Appendix 3: Time and Events Schedule

Event	Screening Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Visit due at week	**Day -14**	**0**	**6**	**14**	**26**	**38**	**52**
		26 week mannitol/control blinded phase				**26 week open label phase**	
Informed Consent [1]	X[1]						
Inclusion/exclusion criteria	X						
Medical History /Demographics	X						
Concomitant medications	X	X	X	X	X	X	X
Physical examination/ vital signs	X	X	X	X	X	X	X
Pulmonary function tests [2]	X	X	X	X	X	X	X
Pregnancy Test[3]	X				X		
Cystic Fibrosis Questionnaire (CFQ-R)	X			X	X		
Health Utilities Index (HUI)	X			X	X		
Pulmonary exacerbations review			X	X	X	X	X
Medical resource use review			X	X	X		
Blood tests	X				X		X
Randomize subject	X						
Administer treatment dose in clinic		X		X	X		
Phone call to subject		X[4]			X[4]		
MTT procedure	X						
Dispense study medication & beta agonist		X	X	X	X	X	
Weigh treatment induced sputum sample		X		X			
Sputum quantitative micro[5]	X		X		X		
Sputum qualitative micro[6]	X	X	X	X	X	X	X
Issue study diary / Collect diary[7]		X			X[7] / X[7]		X
Adverse event assessment		X	X	X	X	X	X
Drug compliance and accountability			X	X	X	X	X
Discharge subject from study							X

1. Consent may be obtained before screening visit but MUST be obtained prior to any protocol procedures being performed.
2. Medications that affect spirometry must be withheld prior to pulmonary function tests
3. Women of childbearing potential only
4. 2 weeks into blinded phase / 4 weeks into open label phase
5. Central lab
6. Local lab
7. If 1st diary is full

15.4 Appendix 4: CFQ-R

Included as PDF attachments:

1) CFQ-R Teen/adult version; English version 2.0
2) CFQ-R Child-self report format; English version 2.0
3) CFQ-R Child-interviewer format; English version 2.0
4) CFQ-R parent version; English version 2.0

Validated language specific translations shall be provide for non-english speaking countries where and if required.

15.5 Appendix 5: Health Utilities Index

Included as PDF attachments:

SELF ASSESSMENT VERSION:
HUI23S1US.15Q September 2, 2002 (Self-complete/administered, Self-assessment, 1-week health-status recall period, US English language version) questionnaire

PROXY ASSESSMENT VERSION:
HUI23P1US.15Q September 2, 2002 (Self-complete/administered, Proxy-assessment, 1-week health-status recall period, US English language version) questionnaire

15.6 Appendix 6: Study Diary

Inhaled Mannitol in Cystic Fibrosis Study Diary

Name:_____

Study Doctor:_____ Ph _____

Study Coordinator:_____ Ph_____

If you are unsure about any requirements in this study, please telephone your study coordinator at the phone number above.

Visit	Appointment Date	Withhold respiratory medications *(see pg 2)*	Sputum sample collected	Bring in study medication *(empty blisters and unused capsules)*	Bring in study diary	Study medication is given in clinic
1		✓	✓			✓
2		✓	✓	✓	✓	
3		✓	✓	✓	✓	✓
4		✓	✓	✓	✓	✓
5		✓	✓	✓	✓	
6		✓	✓	✓	✓	

Please review this diary each day

Table of Contents

MEDICATION WITHHOLDING PERIODS BEFORE YOUR CLINIC VISIT

The medications listed below must be withheld prior to all clinic visits as they may affect your lung function tests (spirometry). If you forget to withhold your medications you should notify your study coordinator to reschedule your appointment.

Medication	Minimum time interval from last dose until spirometry
Mannitol/control	6 to 12 hours
Short acting bronchodilators (isoproterenol, isoetharine, metaproterenol, albuterol, levalbuterol, terbutaline) (e.g. Proventil® or Ventolin®)	6 hours
Inhaled anticholinergics or combination products (e.g. Atrovent® or Combivent®)	12 hours
Long acting β_2 agonists *e.g. salmeterol; efomoterol*(e.g. Serevent® or Foradil®)	12 hours
Medium acting bronchodilators e.g. Ipratropium	12 hours
Oral bronchodilators e.g. Theophylline abd β-agonist tablets	12 hours
ICS LABA combinations *e.g. fluticasone and salmeterol, budesonide and efomoterol*(e.g. Advair®)	12 hours

ORDER OF DAILY PROCEDURES

The recommended order of treatment procedures is:

1. short acting bronchodilator *(reliever medication)*
2. mannitol/control
3. physiotherapy / exercise*
4. rhDNase
5. inhaled antibiotics
6. inhaled cortico-steroids

} *Only if you take them*

*When possible, individual physiotherapy and exercise (if used as a substitute to physio) techniques and regimens should be kept consistent throughout the study.

Page x

Adverse events *Record any health problems that are unusual for you. We would like to know what the problem is, when it started and how long it lasted for. If you took any medicine to treat it, we would like to know this as well.*

Health Problem	**Date / time started**	**Date / time finished**	**How did you treat the problem**	**Was the problem mild, moderate or severe?** (see below *)
Eg: sprained ankle	*23 Mar 07*	*26 Mar 07*	*Pain relief*	*moderate*

*** Mild - you are aware of the sign or symptom but easily tolerated**
Moderate – the discomfort causes interference with your usual activity
Severe - incapacitating, or unable to do usual activities

page x

Medicines: *If you take any new medicines or change the amount of medicine you are already taking please record it below. We would like to know when you started taking this medicine, when you stopped, how much you took and why you took it. Do not include mannitol/control.*

Medicine	Date started	Date finished	How much did you take?	Why did you take it?
Eg Tylenol 8 hour	*23 March 07*	*24 March 07*	*2 caps every 8 hours*	*Sprained ankle*

Community Visits *(do not include hospital visits)*

Doctors, Nurses, Physiotherapists Visits

If you visit the doctor, nurse or physiotherapist for any reason, we would like to know when, where and why you went.

Who did you visit? **1. Hospital doctor (specialist)** **2. Family physician (FP)** **3. Nurse** **4. Physiotherapist** **5. Other health care professional (specify)**	**Type of contact?** **1. Home visit** **2. FP's surgery** **3. Phone call** **4. other (specify)**	**Date of visit**	**Why did you have this visit?**	**Did you have any procedures done?** **Chest X-ray, blood draw, abdominal ultrasound, etc**
2. FP	2. FP's surgery	24th March 2007	Sprained ankle	ankle X-ray

Hospital Visits: *If you go to the hospital for any reason we would like to know about it. This includes visits when you are admitted to hospital or attend as an outpatient, or as a day only admission.*

Type of hospital visit	Date (s)	Reason	Procedures	Hospital	Doctor
Admission *(overnight stay of 1 night or more)*	*1st June 2007 – 5th June 2007*	*Abdominal Pain*	*Abdo ultrasound Abdominal X-ray IV fluids Appendectomy*	*St Elsewhere*	*Dr Who*
Day case *(admitted but discharged same day)*	*6th July 2007*	*Wisdom tooth extraction*	*IV antibiotics IV sedation*	*St Beenthere*	*Dr What*
Outpatient *(seen in clinic or emergency dept)*	*31st August 2007*	*CF check-up*	*Lung function tests, physical exam, throat swab*	*St Notgonthere*	*Dr When*

Pharmacists Visits: *If you visit the pharmacist to have a prescription filled or buy any over the counter medicines, we would like to know about them.*

Medicine	Date	How much did you buy?
Amoxicillin Capsules	*17th August 2006*	*1 pack of 500mg*

15.7 Appendix 7: Sample Size Assumptions and Calculations

A total sample size of 300 patients is planned for the CF-302 study. 180 patients will be randomized to receive inhaled mannitol, while 120 will be randomized to receive control therapy. It is estimated that approximately 65% of subjects will be taking rhDNase. With a drop out rate of 30%, 126 patients in the mannitol arm are expected to complete the study (84 taking rhDNase, 42 not taking rhDNase), and 84 patients in the control arm are expected to complete the study.

The primary hypothesis, that there is no difference in the change from baseline FEV_1 (ΔFEV_1), between patients taking inhaled mannitol and patients in the control group, will be analyzed using a repeated measures analysis. Age and baseline % predicted FEV_1 will be included in the model as covariates for each patient.

The CF-201 phase II study findings are used as assumptions for determining the power for testing this hypothesis, given the sample size chosen. The ΔFEV_1 for patients taking RhDNase and inhaled mannitol ($N \geq 80$) is expected to be 120ml (SD=200), while the ΔFEV_1 for patients in the control arm ($N \geq 80$) is expected to be 0ml (SD=200). Given these assumptions, and a type one error rate of 5%, the power to detect a difference of 120ml in ΔFEV_1 is 96%. When both rhDNase taking and non-rhDNase taking patients are taken into consideration ($N \geq 120$ in the mannitol arm and $N \geq 80$ in the control arm), the power to detect the same difference of 120ml in ΔFEV_1 is 98%.

The power estimate provided is obtained from the formula for the sample size:

$$N_{Control} = \frac{2\sigma^2 \left(z_\alpha + z_\beta\right)^2}{\Delta^2} \qquad 1$$

In formula 1, Δ represent the expected difference in ΔFEV_1 between patients in the mannitol arm and the control arm (120ml). The value σ represent the common standard deviation (200ml). The values Z_α and Z_β represent values of the standard normal distribution that correspond to a type I error rate of α=0.025 and a type II error rate of 1-β, respectively.

The formula can be reworked to solve for Z_β, and thereby determine the power, β:

$$z_\beta = \left(\frac{N_{Control} \times \Delta^2}{2\sigma^2} - z_\alpha{}^2 \right) \left(\frac{1}{1 + 2z_\alpha} \right) \qquad 2$$

Using formula 2, it can be shown that, by having 45 patients taking rhDNase in the mannitol arm, and 45 patients in the control group, a power of 80% is achieved.

Pulmonary Exacerbations

Pulmonary exacerbation rates represent a secondary endpoint of interest. The definition of exacerbation varies between studies, and so it is difficult to find consistent estimators of the number of events and the

time to first event/symptom. The assumptions made in this section are based upon a study of hypertonic saline in patients with cystic fibrosis[35]. Among 83 patients taking 'active' therapy, an average of 0.39 exacerbations (requiring IV antibiotic therapy) per patient were observed, whilst among 81 patients taking 'control' therapy, 0.89 exacerbations per patient were observed. Assuming full patient follow-up in this 48 week study, this corresponds to rates of 0.42 events per patient-year in the 'active' group and 0.96 events per patient-year in the 'control' group. The rate ratio is 0.42/0.96=0.44.

The rate of exacerbation events per patient-year are assumed to be distributed as independent Poisson processes. Calculation of the sample size required to detect this difference in rates is formulated as follows:

$$N = ((1/\lambda_1 + 1/\lambda_2) \times (Z_\alpha+Z_\beta)^2) / (\ln\lambda_1 - \ln\lambda_2)^2$$

where λ_i is estimated event rate in group i. The values Z_α and Z_β represent values of the standard normal distribution that correspond to a type I error rate of α=0.025 and a type II error rate of β=0.2 (corresponding to statistical power of 80%), respectively. Using estimates of $\lambda_1 = 0.42$, $\lambda_2 = 0.96$, and directly computed values of Z_α=1.960 and Z_β=0.842, with 79 patients, each followed for 26 weeks, there is 80% power to detect the difference in exacerbation rates.

16 SIGNATURE PAGES

Protocol DPM-CF-302

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principals stated in the latest version of the Declaration of Helsinki (as nationally acceptable), Good Clinical Practice (GCP) and local regulations (as applicable). I agree to report all information or data in accordance with the protocol, and in particular, I agree to report any serious adverse events. I will accept the monitors', auditors', and regulatory inspectors' oversight of the study. I will abide by the publication plan set forth in the investigator agreement with Pharmaxis. I will promptly submit the protocol to the applicable ethical review board. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in this study.

Clinical Site: _____

Site Number: _____

Site Principal Investigator:

_____ _____
Print Name Title

_____ _____
Signature Date

Accepted for the Sponsor – Pharmaxis Ltd:

_____ _____
Print Name Title

_____ _____
Signature Date

Accepted for the Sponsor's Representative *(if applicable)* _____
Organization Name

_____ _____
Print Name Title

_____ _____
Signature Date

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

3rd July 2012

Contents

List of Tables

List of Figures

List of abbreviations

ACD	Appraisal Consultation Document
Bcc	Burkholderia cepacia complex
BD	Bi-daily
BIDA	Bronchitol Initiation Dose Assessment
BMI	Body mass index
BSC	Best Supportive Care
CF	Cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire – Revised
CI	Confidence Interval
CUA	Cost Utility Analysis
DBP	Double Blind Phase
ERG	Evidence Review Group
FEV1	Forced Expiratory Volume in the first second
HR	Hazard ratio
HUI	Health Utility Index
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
LYG	Life years gained
MS	Manufacturer submission
MTT	Mannitol Tolerance Test
NA	Not applicable
OLEP	Open Label Extension Phase
OLP	Open Label Phase
PA	Pseudomonas aeruginosa
PDPE	Protocol defined pulmonary exacerbations
Pred	Predicted
QALY	Quality-adjusted life year
QoL	Quality of Life
Resp	Respiratory
rhDNase	Recombinant Human Deoxyribonuclease
RR	Relative risk
SD	Standard Deviation
UK	United Kingdom
US	United States
VIF	Variance inflation factors
WTP	Willingness to pay

1 Introduction

As part of the manufacturers' response to the preliminary ACD, the original cost-utility analysis (CUA) provided as part of the manufacturer's submission (MS: February, 2011) has been updated to reflect the comments received by the ERG and the Committee.

To reflect the comments received by NICE and the needs of the CF community, the manufacturer has identified two CF patient populations who have the most unmet medical need and in which inhaled mannitol provides a significant clinical benefit.

- Patients receiving Best Supportive Care (BSC) without add-on rhDNase.
- Patients receiving BSC (+/- rhDNase) experiencing a greater than 2% decline in FEV1 percent predicted per year.

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.

This report documents the modifications made to the CUA for the first base case (non-users), and includes details of the evidence and analysis used to underpin the revisions, as well as relevant sensitivity and scenario analysis tested to examine the influence of the changes to the ICER results. In the interests of transparency, a copy of the model developed in TreeAge Pro 2009 is also provided. Unless otherwise stated, all other parameters are as per previously provided in the MS or clarification responses to the ERG.

2 Revised model

This section lists the parameters and characteristics of the model that are modified, based on the ERG comments received. Details on each of the modifications are provided in sections 2.1 to 2.5.

- The cost-effectiveness of Bronchitol has been analysed in adult CF patients, when added as a treatment for patients currently receiving BSC without rhDNase (non-users).
- The analysis incorporates a new responder definition (0% improvement in FEV1 percent predicated at 6 weeks) to enable ease of implementing a stopping rule in clinical practice;
- In acknowledging the comments of the ERG, the model framework as been modified to reflect treatment-independent, costs and utilities for respiratory symptom improvement, when valuing health states;
- Relevant clinical and effectiveness input parameters have been adapted to the new target population;
- The outcomes at 26 weeks were carried forward for the next 4 cycles in the model (48 weeks) unless the patient died;
- Bronchitol responders are allowed to discontinue treatment. All drop-outs are switched to best supportive care;
- Costs of rhDNase (Pulmozyme®) have been changed from £16.88 to the most recent price of £16.55 (BNF 63);
- Costs of Bronchitol® have also been updated to £16.55 and the cost for the Bronchitol initiation dose assessment (BIDA) test is now considered on an ITT basis;
- The annual exacerbation rate for patients in the control group has been recalculated according to the proposed ERG methodology;
- The hazard ratio for FEV_1 % predicted is now based on a Cox model with only FEV_1 % predicted as explanatory variable;
- Patients with missing data from the Quality of Life instrument (CFQ-R) were considered as "not improved in respiratory symptoms;

- 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;
- Parameters of the beta distribution for a utility decrement due to exacerbation have been adjusted;
- 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;
- Parameters of the gamma distributions of the cost estimates have been adjusted to reflect second order uncertainty.

2.1 Model structure

No modifications to the core model structure have been performed 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. Full details of the model structure are presented in sections 6.2.2 to 6.2.6 in the manufacturer submission.

The key features of the analysis are presented in Table 1 below.

Table 1 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Life time (Theoretic maximum of 100 years)	Chronic progressive disease	Guide to the methods of technology appraisal
Cycle length	First cycle 6 weeks, second cycle 8 weeks, subsequent cycles 12 weeks	Availability and best fit to data and clinical practice	Guide to the methods of technology appraisal
Half-cycle correction	0	Cycle length too short to require correction	Guide to the methods of technology appraisal
Were health effects measured in QALYs; if not, what was used?	QALYs		Guide to the methods of technology appraisal
Discount of 3.5% for utilities and costs	3.5% for utilities and costs		Guide to the methods of technology appraisal
Perspective (NHS/PSS)	NHS and PSS		Guide to the methods of technology appraisal
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

2.2 Population

The Bronchitol studies show a clinical benefit of Bronchitol in all adult CF patients irrespective of rhDNase use. However, the treatment effect of Bronchitol in lung function and pulmonary exacerbations tended to be higher in patients not on rhDNase. This patient subset is likely to benefit the most from Bronchitol treatment.

2.3 Treatment effectiveness

2.3.1 Treatment independent parameters

Baseline patient characteristics

The baseline patient characteristics from the pooled adult rhDNase non-users population are used in the model are well balanced (Table 2).

Table 2 Baseline patient characteristics

Parameter	Bronchitol	Control	Total
N	49	85	134
Gender (% female)	42.9%	36.5%	38.8%
Age (years)	29.8	30.9	30.5
BMI (kg/m^2)	22.5	23.3	23.0
FEV_1 % predicted	61.0	62.6	62.0

Natural decline in FEV_1% predicted

The rate of lung function decline in CF patients over time was estimated using Australian observational data provided by BioGrid. As detailed in the MS, a repeated measures mixed model analysis was undertaken to estimate the mean rate of decline of FEV_1 % predicted over time as a function of covariates such as age, gender, BMI and of inpatient hospital admission days per quarter. To this end, for each patient in the database and in each calendar quarter, the highest measured FEV_1 % predicted was recorded. The covariance structure resulting from the repeated measures mixed model was used in the Cholesky decomposition technique to provide correlated draws from a multivariate normal distribution for the probabilistic sensitivity analysis.

There was no modification regarding the rate of lung function decline compared with the initial manufacturer submission. The final model results are presented in Table 67 and appendix 16 in the manufacturer submission.

Probability of severe exacerbation in CF population

Due to the lack of information on exacerbations in the BioGrid database, the number of inpatient hospital admissions per quarter was used as a proxy for the rate of exacerbations (see Table 3). As described in the manufacturer's response, exacerbations reflect 95% of the hospital admissions, and the remaining 5% of admissions are likely to reflect a severe change in the disease which a minor exacerbation would trigger).

Table 3 Hospitalisation rate in BioGrid data

Patient population	Hospital Days/Quarter				#PTS with hospital days:			
	0		>0		0	>0	All	
	#quarters	%	#quarters	%	N	N	N	Rate
Adults	5,669	72%	2,202	28%	1,634	1,170	2,804	1.112
Adults<=30 years	3,979	75%	1,344	25%	1,190	729	1,919	1.010
Adults>30 years	1,690	66%	858	34%	444	441	885	1.347

Source: BioGrid Australia 2010

The pulmonary exacerbation rate used in the model was the rate observed in adults under the age of 30 years (1.010 per year). This rate was calculated by considering the 1344 quarters with a hospitalisation as the number of event (assuming that no more than one hospitalisation occurs per quarter), and dividing this by the total number of observed quarters (3,979+1,344=5,323). The resulting event rate was 0.252 per patient quarter that is 1.010 per patient-year. For patients aged 30 or above this was corrected by applying a relative risk of 1.334 (1.347/1.010) the baseline risk (see clarification notes relating to cohort lung function decline by age within the manufacturer's response).

Finally the exacerbation rate was increased for patients who experienced a pulmonary exacerbation in the previous 48 weeks by applying a relative risk of 1.59 (see section 6.3.1 of the manufacturer submission).

Probability of lung transplantation

No modification compared to the initial manufacturer's submission has been applied.

CF Mortality

Cystic fibrosis patients have lower life expectancy than the general community. Mortality has been linked to lung function decline and experience of exacerbations, as well as a number of factors including BMI and specific respiratory infections. BioGrid data was used to explore predictors of mortality. A Cox's proportional hazard survival model for CF survival from birth to CF-related death was developed for this purpose. Since FEV_1 was the primary outcome of the Bronchitol pivotal trials, particular focus was payed on the relationship between FEV_1 and survival. Other potential risk factors, like exacerbations, gender and BMI were also investigated. If these factors were not significant (at 0.05 significance level) they were dropped from the final model. Table 4 presents the hazard ratio used in the cost-effectiveness model. Note that FEV_1 % predicted was included as time varying covariates in the model.

Table 4 BioGrid analysis of survival (Adults only)

Analysis of 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

Source: BioGrid Australia 2010

Excess mortality due to exacerbation and Bcc infection

No modification compared to the manufacturer's submission has been applied.

Transplantation mortality

No modification compared to the manufacturer's submission has been applied.

Non-CF mortality

No modification compared to the manufacturer's submission has been applied.

2.3.2 Treatment dependent parameters

Effect of treatment on FEV_1 % predicted

A linear regression analysis was performed to obtain a prediction of the FEV_1 % predicted at the end of the trial follow-up period, i.e. week 26. The final model is presented in Table 5 below and details are given in Appendix A. The covariance structure resulting from the regression model was used in the Cholesky decomposition technique to provide correlated draws from a multivariate normal distribution for the probabilistic sensitivity analysis.

Table 5 Linear regression model for FEV_1 % predicted at week 26 (Adult rhDNase non-users)

Variable	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	0.67561	2.93364	0.23	0.8182
Treatment group	1.12080	1.28222	0.87	0.3838
FEV_1 % predicted at baseline	0.93068	0.04337	21.46	<.0001
Responder	6.67049	1.33887	4.98	<.0001

The double blinded treatment period in both clinical trials was 26 weeks. Bronchitol is intended for lifetime use hence the results of the trials need to be extrapolated over the life time of a patient. It is therefore assumed that a benefit in lung function achieved in the first six months will continue to be received over the patient's lifetime, assuming that he/she will receive therapy for the remainder of his life.

The extension trials of CF301 and CF302 (pg 91 of MS) demonstrated that the treatment benefit of Bronchitol is maintained for up to the 78 weeks. Furthermore, patients who had been on control during the double-blind phase and were switched to Bronchitol in the extension phases showed a significant improvement in lung function of a magnitude similar to that observed for Bronchitol-treated patients in the double-blinded studies. Given the results, it is reasonable to assume that patients receiving Bronchitol and responding to treatment after 6 weeks are likely to retain their treatment benefit to at least 78 weeks. To incorporate this clinical data into the CUA, the outcomes at 26 weeks were carried forward for the next 4 cycles in the model (48 weeks) unless the patient died.

Effect of treatment on pulmonary exacerbations

Treatment with Bronchitol has an impact on the pulmonary exacerbation rate. The rate ratio of having a PDPE for patients who respond to Bronchitol was calculated as the observed difference in PDPE rate in patients who responded to Bronchitol over the PDPE rate for the overall Control group. The values used in the economic evaluation are presented in Table 6 below.

Table 6 PDPE rates from combined DMP-CF-301 and DMP-CF-302 (Adult rhDNase non-users)

	Control			Bronchitol	
	Non-responder	**Responder**	**Total**	**Non-responder**	**Responder**
N	22	27	49	26	59
Number of PDPEs	9	8	17	9	8
Years of exposure	9.68	13.25	22.93	8.80	27.12
Annual Rate	0.93	0.60	0.74	1.02	0.30
Rate Ratio*					0.40

* The rate ratio was calculated based on the annual exacerbation rate observed in Bronchitol responders compared to the overall Control arm.

In each treatment arm, the risk of having a pulmonary exacerbation was adjusted for patients with a history of exacerbations based on the observed elevated risk of exacerbation for patients who had experienced at least one exacerbations in the year preceding their entry to the DPM-CF-302 study (RR=1.59, p<0.001). The annual exacerbation rate was based on BioGrid data (see Table 3).

Patient response

It is not realistic to assume that the patients will continue treatment with Bronchitol for the rest of their life irrespective of whether there is a benefit or not. Clinicians are not likely to prescribe treatment to those patients who get no benefit. Therefore a continuation rule was implemented in the Bronchitol arm in the cost-effectiveness analysis. Only responders to Bronchitol continued on this agent.

Response to treatment is defined as a relative increase of at least 0% in the FEV_1 predicted at week 6 from baseline. This definition is in line with the opinion of the Interviewed European experts who stated that any increase in FEV_1 predicted in CF patients is clinically meaningful since in these patients FEV_1 predicted is constantly declining towards premature death in CF patients. Table 7 below provides the transition probability of remaining on Bronchitol treatment after 6 weeks.

Table 7 Probability of being a responder to Bronchitol from DMP-CF-301 and DMP-CF-302 (Adult rhDNase non-users)

	Bronchitol			Control		
	n	N	%	n	N	%
Responder	59	85	69.4%	27	49	55.1%

In the model it is assumed that patients on Bronchitol who are non-responders will discontinue the treatment with Bronchitol and will be switched to best supportive care which is identical to the Control arm. Patients continuing to receive Bronchitol would have a maintained benefit.

Furthermore, it is assumed that only a percentage of Bronchitol responders according to the above definition will continue treatment for the rest of their life. These patients may discontinue treatment due to other reasons such as poor compliance or lost to follow-up. The percentage of patients withdrawing from the double blind and the open label phases of the DPM-CF-301 and DPM-CF-302 studies are presented in Table 8 below.

Table 8 Probability of Bronchitol responders switching due to treatment withdrawal (Adult rhDNase non-users)

Visit	n	N	%
Visit 3 (Week14)	5	59	8%
Visit 4 (Week 26)	3	54	6%
Visit 5 (Week 38)*	2	43	5%
Visit 6 (Week 52)	6	41	15%
Visit 7 (Week 64)**	2	13	15%
Visit 8 (Week 78)	0	11	0%

* N represents the number of Bronchitol responders who entered the OLP phase
** N represents the number of Bronchitol responders who entered the OLEP phase

These probabilities were converted to an annual rate and the average was taken to determine the annual drop-out rate in the model. In the model all drop-outs are considered to switch to control.

Improvement respiratory symptoms

The transition probabilities for improved respiratory symptoms are calculated from the pooled -CF-301 and DMP-CF-302 data.

At baseline all patients start in the CF health state and are assumed to remain there till the end of cycle 2 (corresponding to the 14-week visit). The probability of moving to the “improved respiratory symptoms” at this point was based on the number of patient with ≥4 points improvement in their CFQ-R respiratory domain score. The probability of remaining in the “improved respiratory symptoms” health at each next cycle of 12 weeks was based on the number of patients who maintained a ≥4 points improvement in the CFQ-R respiratory domain score at the 26-week visit compared to baseline. Similarly the probability of moving to the “improved respiratory symptoms” at each next cycle was based on the percentage of patients who had <4 points improvement in the CFQ-R respiratory domain score at the 14-week visit and a ≥4 points improvement in the CFQ-R respiratory domain score at the 26-week compared to baseline (see Table 9). Patients with missing CFQ-R data were considered as not improved in respiratory symptoms.

Table 9 Transition probabilities improvement in respiratory symptoms

Treatment	Respiratory Symptoms	n	N	%
Bronchitol	Improved after 3 months	33	85	39%
	Remain improved after 6 months	23	33	70%
	Improved after 6 months but not at 3 months	8	52	15%
Control	Improved after 3 months	24	49	49%
	Remain improved after 6 months	18	24	75%
	Improved after 6 months but not at 3 months	1	25	4%

2.3.3 Summary of variables applied in the economic model

The list of variables included in the cost-effectiveness analysis and information whether they have changed since the original model in the manufacturer submission are provided in tables 10 to 16. Although the variables for the decline in lung function did not change, for completeness we present these variables in Table 15 and Table 16.

Table 10 Summary of variables applied in the economic model: patient population

Variable name	Variable description	Value	Distribution	Modified
Gender	Gender CF patient (% male)	0.61	Beta n = 134, r = 82	Yes
Age_start	Age CF patient at baseline	30.51	Sample from table "AgeCFpt"	Yes
BMI_start	BMI CF patient at baseline	23.04	Sample from table "bmiCFpt"	Yes
FEV_start	FEV_1 % predicted CF patient at baseline	62.00	Sample from table "FEV1_CFpt"	Yes
Bcc_infection	Prevalence of Bcc infection (age 16+)	0.05	Beta n = 3081, r = 160	No

Table 11 Calculation of treatment effect

Variable name	Variable description	Formula
FEV_V4_B_improvRS	FEV_1 % predicted after 26 weeks of treatment with Bronchitol in patients having improvement in respiratory symptoms	fParameter_intercept+BMI_start*fParameter_BMI+FEV_start*fParameter_FEV1+1*fParameter_Bronchitol+1*fParameter_improvRS+tResponderBw6*fParameter_responder+tExacerbation*fParameter_PDPE
FEV_V4_B_no_improvRS	FEV_1 % predicted after 26 weeks of treatment with Bronchitol in patients not having improvement in respiratory symptoms	fParameter_intercept+BMI_start*fParameter_BMI+FEV_start*fParameter_FEV1+1*fParameter_Bronchitol+0*fParameter_improvRS+tResponderBw6*fParameter_responder+tExacerbation*fParameter_PDPE
FEV_V4_C_improvRS	FEV_1 % predicted after 26 weeks of treatment with Control in pts having improvement in respiratory symptoms	fParameter_intercept+BMI_start*fParameter_BMI+FEV_start*fParameter_FEV1+0*fParameter_Bronchitol+1*fParameter_improvRS+tResponderC*fParameter_responder+tExacerbation*fParameter_PDPE
FEV_V4_C_no_improvRS	FEV_1 % predicted after 26 weeks of treatment with Control in patients not having improvement in respiratory symptoms	fParameter_intercept+BMI_start*fParameter_BMI+FEV_start*fParameter_FEV1+0*fParameter_Bronchitol+0*fParameter_improvRS+tResponderC*fParameter_responder+tExacerbation*fParameter_PDPE

Table 12 Summary of variables applied in the economic model: treatment effect

Variable name	Variable description	Value	Distribution	Modified
fParameter_intercept*	Parameter estimate of intercept*	0.676	Multivariate Normal, using Cholesky decomposition	Yes
fParameter_BMI*	Parameter estimate of BMI*	0	NA	Yes
fParameter_FEV1*	Parameter estimate of FEV_1 % predicted at baseline*	0.931	Multivariate Normal, using Cholesky decomposition	Yes
fParameter_Bronchitol*	Parameter estimate for treatment with Bronchitol*	1.121	Multivariate Normal, using Cholesky decomposition	Yes
fParameter_improvRS*	Parameter estimate for improvement in respiratory symptoms used to predict the FEV_1 % predicted after 26 weeks of treatment*	0	NA	Yes
fParameter_responder*	Parameter estimate for response to treatment*	6.670	Multivariate Normal, using Cholesky decomposition	Yes
Responder B	Probability of being a responder to Bronchitol	0.69	Beta n = 85, r = 59	Yes

Variable name	Variable description	Value	Distribution	Modified
Responder C	Probability of being a responder to Control	0.55	Beta n = 49, r = 27	Yes
rdropoutB	Annual drop-out rate for the Bronchitol responders	0.390	Beta alpha = 6.732, beta = 10.521	Yes
nbwsustB	Number of cycles that responders on Bronchitol carry forward FEV1pp from w26	4	NA	Yes

* Parameter estimate in multivariate regression model for FEV_1 % predicted after 26 weeks

Table 13 Summary of variables applied in the economic model: pulmonary exacerbations

Variable name	Variable description	Value	Distribution	Modified
RR_ExacerbationB_responder	Relative risk exacerbation with Bronchitol (patients who respond to treatment)	0.398	Log-Normal u (mean of logs) = -0.921 sigma (std dev of logs) = 0.429	Yes
RR_Exacerbation_over30	Relative risk for patient experiencing an exacerbation over the age of 30	1.335	Log-Normal u (mean of logs) = 0.288, sigma (std dev of logs) = 0.044	Yes
RR_previous_exacerbation	Relative risk of experiencing an exacerbation if patient has experienced an exacerbation in the previous year.	1.594	Log-Normal u (mean of logs) = 0.4637 sigma (std dev of logs)= 0.0688	Yes
dExacerbation_base	Exacerbation rate control group per quarter	0.252	Beta n = 5,323, r = 1,344	Yes

Table 14 Summary of variables applied in the economic model: respiratory symptoms

Variable name	Variable description	Value	Distribution	Modified
dImprovedRS_C_v3	Probability of improved respiratory symptoms at week 14 (V3) for pts treated with Control	0.490	Beta n = 49, r = 24	Yes
dImprovedRS_C_v4	Probability of improved respiratory symptoms at week 26 (V4) for Control pts	0.040	Beta n = 25, r = 1	Yes
dRemainImprovRS_C_v4	Probability of continuing to have improved respiratory symptoms at week 26 (V4) for pts treated with Control	0.750	Beta n = 24, r = 18	Yes
dImprovedRS_B_v3	Probability of improved respiratory symptoms at week 14 (V3) for pts treated with Bronchitol	0.388	Beta n = 85, r = 33	Yes

Variable name	Variable description	Value	Distribution	Modified
dImprovedRS_B_v4	Probability of improved respiratory symptoms at week 26 (V4) for Bronchitol pts	0.154	Beta n = 52, r = 8	Yes
dRemainImprovRS_B_v4	Probability of continuing to have improved respiratory symptoms at week 26 (V4) for pts treated with Bronchitol	0.697	Beta n = 33, r = 23	Yes

Table 15 Summary of variables applied in the economic model: decline in FEV_1 % predicted

Variable name	Variable description	Value	Distribution/Formula	Modified
fParameter_age	Parameter estimate for age*	-1.02	Multivariate Normal, using Cholesky decomposition	No
fParameter_ageplus30	Parameter estimate for age over 30*	1.65	Multivariate Normal, using Cholesky decomposition	No
fParameter_exacerbation	Parameter estimate for exacerbation*	-2.08	Multivariate Normal, using Cholesky decomposition	No
rFEVdecline	Annual change in FEV_1 % predicted in patients aged 30 or below without an exacerbation	-1.02	fParameter_age+0*fParameter_ageplus30+0*fParameter_exacerbation	No
rFEVdecline_exacerbation	Annual change in FEV_1 % predicted in patients aged 30 or below who had an exacerbation	-3.10	fParameter_age+0*fParameter_ageplus30+1*fParameter_exacerbation	No
rFEVdecline_exacerbation_plus30	Annual change in FEV_1 % predicted in patients aged over 30 who did not have an exacerbation	-1.44	fParameter_age+1*fParameter_ageplus30+1*fParameter_exacerbation	No
rFEVdecline_plus30	Annual change in FEV_1 % predicted in patients aged over 30 who had an exacerbation	0.64	fParameter_age+1*fParameter_ageplus30+0*fParameter_exacerbation	No

***** Parameter estimates mixed model for FEV_1 % predicted

Table 16 Summary of variables applied in the economic model: mortality

Variable name	Variable description	Value	Distribution	Modified
RR_Bcc	Relative risk of death due to a Bcc infection in combination with an exacerbation	3.410	LogNormal u (mean of logs) = 1.2267 sigma (std dev of logs) = 0.5862	No
HR_FEV	Hazard rate $ppFEV_1$	0.952	LogNormal u (mean of logs) = -0.04919, sigma (std dev of logs) = 0.0067	Yes

2.4 Health related quality of life

In the cost-effectiveness analysis the HUI2 global utility scores are determined for the "Cystic fibrosis" health state for Bronchitol and control.

The values used as inputs for the model are determined as follows:

- The baseline utility is the average overall HUI2 global utility score at screening irrespective of the treatment (see Table 71 in MS);
- Next, for each patient the change in utility between Visit 3/Week 14 (or the value reported at the termination visit if the HUI2 global utility value is missing at Visit 3/Week 14) and baseline was calculated. The same was done for the change between Visit 4/Week 26 and baseline;
- The average change in utility from baseline was calculated;
- Finally, the HUI2 global utility scores used into the cost-effectiveness analysis is obtained by summing up the average change and the baseline utility for each health state.

The values used in the cost-effectiveness analysis are presented in Table 17.

Table 17 Summary of quality-of-life values for cost-effectiveness analysis

Variable name	Description	Value	Distribution	Modified
u_base	Distribution baseline utility	0.896	Normal Mean = 0.896, Std Dev = 0.0169	Yes
d_u_improvRS	Change in utility from baseline for patients treated with Bronchitol with improvement in respiratory symptoms	0.025	Normal Mean = 0.025, Std Dev = 0.018	Yes
d_u_no_improvRS	Change in utility from baseline for patients treated with Bronchitol without improvement in respiratory symptoms	0.001	Normal Mean = 0.001, Std Dev = 0.0078	Yes
u_improvRS	Utility patient with improvement in respiratory symptoms	0.921	u_base+d_u_improvRS	Yes
u_no_improvRS	Utility no improvement in respiratory symptoms	0.897	u_base+d_u_no_improvRS	Yes
d_Exacerbation	Duration of utility decrement for exacerbation (days)	13.4	Normal Mean = 13.4, Std Dev = 2.68	Yes
d_u_Exacerbation	Utility decrement for patients experiencing an exacerbation	0.230	Beta alpha = 5.555, beta = 18.597	Yes
u_Exacerbation	Utility decrement for exacerbation	-0.008	-d_u_Exacerbation* d_Exacerbation/365	No

Variable name	Description	Value	Distribution	Modified
u_LT_WL	Utility for patients with FEV<30	0.310	Normal Mean = 0.310, Std Dev = 0.0332	No
u_LT	Utility for lung transplant patients	0.800	Normal Mean = 0.800, Std Dev = 0.0203	No

The duration of the utility decrement for an exacerbation was not reported in literature. As indicated in the ERG report, the conference abstract by Bradley[1], the mean number of hospital days for exacerbations is presented, 9.2 days (n=150). Additionally, on average, patients receive a further 4.2 days IV treatment post-hospitalisation. It seems reasonable to assume that during the period of out-hospital IV treatment, the utility decrement should still be applied. Thus the total duration of the utility decrement is 13.4 days. In addition, the ERG has assumed that a reasonable estimate of the standard error is 20% of the mean, which means an increase in input uncertainty in the probabilistic sensitivity analysis. We have considered the same assumption in the current model.

2.5 Resources and costs

Costs of treatment

The costs of Bronchitol are £16.55 per day, which includes the costs of the inhalation device. In addition, patients are required to undergo a Bronchitol Initiation Dose Assessment (BIDA) designed to assess bronchial hyper-reactivity prior to commencing Bronchitol treatment. In practice 6.9% of patients may not go on to receive Bronchitol treatment on the basis of this test. The costs of this test have been applied on an ITT basis. No administration costs apply.

- Bronchitol Initiation Dose Assessment (BIDA), single use pack containing 10 x 40mg capsules and 1 inhaler is £8.27
- Bronchitol® 14 day pack (14-day treatment pack containing 280 x 40mg capsules and two inhalers) is £231.66 per 14d pack (equivalent to an average of £16.55 per day; £0.83 per capsule).

Health state costs

In this revised model, the total 6-monthly CF costs (including concomitant medications, visits and hospitalisations) were derived by health state (i.e. being improved in respiratory symptoms or not). These costs have been derived for the non-user population.

The cost of an exacerbation was calculated as the difference in 6-months costs between patients who had 1 PDPE during the 26 weeks versus all patients who had 0 PDPE during this period. As we believe the cost of the PDPE itself would not differ if a patient was on Pulmozyme or not, we have used all adult data to calculate this cost (i.e. this remained unchanged from our original submission).

No health state cost other than those presented for patients with CF (with or without improvement in respiratory symptoms) are applicable to the model. Apart from CF treatment, the model includes

transition costs for pulmonary exacerbations and lung transplant. All cost parameters in the model are summarised in Table 18 below.

Table 18 List of health states and associated costs in the economic model

Parameter	Description	Value	Distribution	Modified
c_CF_improvRS	Total 6-monthly cost rhDNase non-user with improved respiratory symptoms	2,307	Gamma, alpha = 41.7513 lambda = 0.0181	Yes
c_CF_no_improvRS	Total 6-monthly cost rhDNase non-user with no improved respiratory symptoms	3,255	Gamma, alpha = 13.0239, lambda = 0.0040	Yes
c_Exacerbation	Cost pulmonary exacerbation	6,115	Gamma, alpha = 21.0388, lambda = 0.0034	Yes
c_LT	Cost lung transplant	35,447	Gamma, alpha = 56.0062, lambda = 0.0016	Yes
c_postLT	Post lung transplant treatment cost	87,424	Gamma, alpha = 251.7824, lambda = 0.0029	Yes

To be noted that for the cost of lung transplant and post-lung transplant, the same assumptions as the ERG's were applied, i.e.:

- For the cost of lung transplant we have assumed that the standard deviation is equal to the mean which resulted in a standard error of 4,738;
- For the post lung transplant treatment cost we have assumed that the standard deviation is equal to 1.65*mean which resulted in a standard error of 5,510.

3 Results

3.1 Clinical outcomes from the model

The reported outcomes for the pooled rhDNase non-user adults in the two Bronchitol, studies and those of the model are presented in Table 19. All results correspond to a time horizon of 26 weeks.

Table 19 Summary of clinical outcomes observed in the Bronchitol studies and in the model

Outcome	Clinical trial result		Model result	
	Control	Bronchitol	Control	Bronchitol
Lung function (FEV_1 % predicted at baseline)	60.99	62.62	62.04	62.04
Change in FEV_1 % predicted	0.40*	3.29*	0.06	2.09
% of patients with ≥1 exacerbations after 26 weeks	31%	15%	43%	28%
Exacerbation rate	0.60	0.47	1.10	0.69
Responder	0.55	0.69	0.56	0.70
Survival	100%	100%	1.00	1.00
% of patients with lung transplant	0%	0%	0.00	0.00
QALYs	0.45	0.45	0.45	0.45

*calculated using mixed model repeated measures analysis of DPM-CF-301 and DPM-CF-302 using imputed height.

Overall the observed clinical trial results correlate well to the modelled result. In the model, patient characteristics at baseline (e.g., gender, age, BMI and FEV_1 % predicted) were identical in each arm, whereas small differences were observed in the clinical trials. The difference between the modelled change in FEV_1 % predicted after 26 weeks of treatment and the observed clinical result relates to the fact that the model predicts the FEV_1 % predicted based on a patient's characteristics rather than implementing the observed change in the clinical trial. As expected, the improvement in FEV_1 % predicted in the Bronchitol arm is lower than in the clinical trial, because in the model, patients are switched to best supportive care (Control) after 6 weeks if they do not respond to Bronchitol treatment. In addition, in the model, even though the patient may be a responders after 6 weeks, patients on Bronchitol can still drop-pout (discontinue treatment) and would be switched to best supportive care (Control).

The model calculations also show a higher number of exacerbations than observed in the clinical trial. The baseline exacerbation rate in the model is taken from BioGrid data instead of the clinical trial. The BioGrid analysis reported a higher exacerbation rate (1.112, see Table 3), although this is likely to be lower than the UK based on observations of 1.5 per year by Jarad *et al. (2008)* [2]. In addition if a patient has a pulmonary exacerbation after 6 weeks, the chance of experiencing an exacerbation after 14 and 26 weeks is increased by a factor 1.59. Similarly patients experiencing a pulmonary exacerbation after 14 weeks have an increased risk of a pulmonary exacerbation after 26 weeks. It should be noted that in using a higher exacerbation rate than in the trial (conservatively reflecting practice in the UK), given the chosen cycle length the model, the extrapolated exacerbation rate over the life time of a patient is still likely to be underestimated in the model as patients would likely have more exacerbations as the lung function declines towards the end-stages of life. Furthermore, and as expected the modelled exacerbation rate for Bronchitol is higher than observed in the BioGrid database because of cross-over to the control arm in cases where the patient does not respond to Bronchitol.

3.2 Base case analysis

The results of the base case analysis are presented in

Table 20. Results are based on 100,000 simulations.

Table 20 Base-case results

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

Table 21 lists the costs, life years and QALYs accrued for treatment responder and non-responders, respectively.

Table 21 Model outputs by clinical outcomes

	Bronchitol		Control	
Outcome	Responder	Non-responder	Responder	Non-responder
Cost	190,418	164,217	180,539	160,497
QALY	10.95	9.47	10.51	9.28
LY	12.32	10.74	11.85	10.54

QALY, quality-adjusted life year; LY, life years

The resource use predicted by the model by category of costs is presented in Table 22.

Table 22 Summary of predicted resource use by category of cost

Item	Cost intervention (Bronchitol)	Cost comparator (Control)	Increment	Absolute increment	% absolute increment
Bronchitol	10,294	0	10,294	10,294	63%
CF costs	72,884	69,535	3,349	3,349	20%
Exacerbation costs	98,098	100,179	-2,081	2,081	13%
LT costs	1,180	1,905	-725	725	4%
Total	182,456	171,619	10,837	16,449	100%

Table 23 Other model outputs

Item	Bronchitol	Control	Increment
Mean time on treatment	17.60	16.33	1.27
Median life expectancy	45.42	44.58	0.85
Median survival	15.27	14.12	1.15
% LT	0.013	0.020	

Median survival in the model was 14.1 years for Control versus 15.3 years for Bronchitol, and median life expectancy was 43.4 versus 44.6 years, respectively. The reported median life expectancy in the UK registry is as expected lower (38.8 years), as the registry includes children.

3.3 Sensitivity analyses

3.3.1 Deterministic sensitivity analysis

The parameters which have been subjected to deterministic sensitivity analysis are presented in Table 24 . The only parameter that has been omitted is the background mortality rate.

The results of the one way sensitivity analysis are presented in Table 24. Results are based on 100,000 simulations. The most sensitive parameters are also showed in Figure 1.

Table 24 Results deterministic sensitivity analysis

Variable	Min	Max	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Base case	0.00	0.00	10,837	0.54	19,993	10,837	0.54	19,993
Baseline patient characteristics								
Age CF patient at baseline	18.00	56.00	11,006	0.58	18,915	7,911	0.40	19,876
BMI CF patient at baseline	17.00	30.00	10,864	0.54	19,993	10,864	0.54	19,993
FEV1 % predicted CF patient at baseline	40.00	90.00	5,818	0.44	13,161	8,188	0.38	21,456
Percentage of male CF patients	0.00	1.00	9,077	0.46	19,837	8,498	0.43	19,923
Percentage of patients with chronic Bcc infection	0.00	0.09	10,724	0.54	19,980	10,841	0.54	20,009
Responder								
Percentage of CF patients responding to Bronchitol treatment	0.59	0.79	8,113	0.39	20,843	13,468	0.69	19,588
Percentage of CF patients responding to Control treatment	0.41	0.69	13,816	0.72	19,105	8,020	0.37	21,685
Improvement in respiratory symptoms								
Probability of improvement in respiratory symptoms after 14 weeks for pts treated with Bronchitol	0.29	0.49	10,934	0.54	20,154	10,794	0.54	19,832
Probability of improvement in respiratory symptoms after 26 weeks for pts treated with Bronchitol	0.07	0.26	11,290	0.54	20,985	10,477	0.55	19,107
Probability of improvement in respiratory symptoms after 14 weeks for pts treated with Control	0.35	0.63	10,723	0.55	19,667	11,004	0.54	20,317
Probability of improvement in respiratory symptoms after 26 weeks for pts treated with Control	0.00	0.14	10,666	0.55	19,540	11,159	0.54	20,673
Probability continuing to have improved respiratory symptoms for pts treated with Bronchitol	0.53	0.84	11,159	0.54	20,677	10,424	0.55	18,987
Probability continuing to have improved respiratory symptoms for pts treated with Control	0.56	0.90	10,726	0.55	19,610	11,277	0.54	20,878

Variable	Min	Max	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Estimated FEV1 at week 26								
Cholesky decomposition method for intercept used to predict the FEV1 % predicted after 26 weeks of treatment	-5.07	6.43	8,018	0.44	18,402	9,087	0.44	20,727
Cholesky decomposition method for Bronchitol treatment used to predict the FEV1 % predicted after 26 weeks of treatment	-1.39	3.63	783	-0.04	-20,440	16,659	0.91	18,396
Cholesky decomposition method for % predicted FEV1 used to predict the FEV1 % predicted after 26 weeks of treatment	0.85	1.02	8,534	0.45	19,170	8,964	0.44	20,528
Cholesky decomposition method for responder used to predict the FEV1 % predicted after 26 weeks of treatment	4.05	9.29	7,398	0.37	20,195	9,773	0.50	19,653
Annual drop-out rate for the Bronchitol responders	0.00	1.25	23,018	1.33	17,274	8,798	0.44	19,958
Number of cycles that patients on Bronchitol maintain the FEV1pp from w26	0.00	8.00	10,290	0.51	20,280	11,362	0.57	19,844
Decline in lung function								
Annual change in ppFEV1 in patients aged 30 or below without an exacerbation	-1.40	-0.63	10,995	0.56	19,750	10,940	0.54	20,251
Annual change in ppFEV1 in patients aged 30 or below who had an exacerbation	-4.58	-1.62	11,404	0.58	19,534	10,489	0.51	20,521
Annual change in ppFEV1 in patients aged above 30 who had an exacerbation	-3.82	0.94	10,159	0.53	19,320	10,655	0.52	20,306
Annual change in ppFEV1 in patients aged above 30 without an exacerbation	-0.65	1.92	9,127	0.47	19,606	12,268	0.61	19,964
Cholesky decomposition method for age used to calculate decline in FEV1 % predicted	-1.40	-0.63	10,326	0.53	19,427	11,258	0.55	20,376
Cholesky decomposition method for age over 30 used to calculate decline in FEV1 % predicted	0.76	2.55	9,556	0.49	19,481	11,762	0.59	20,072

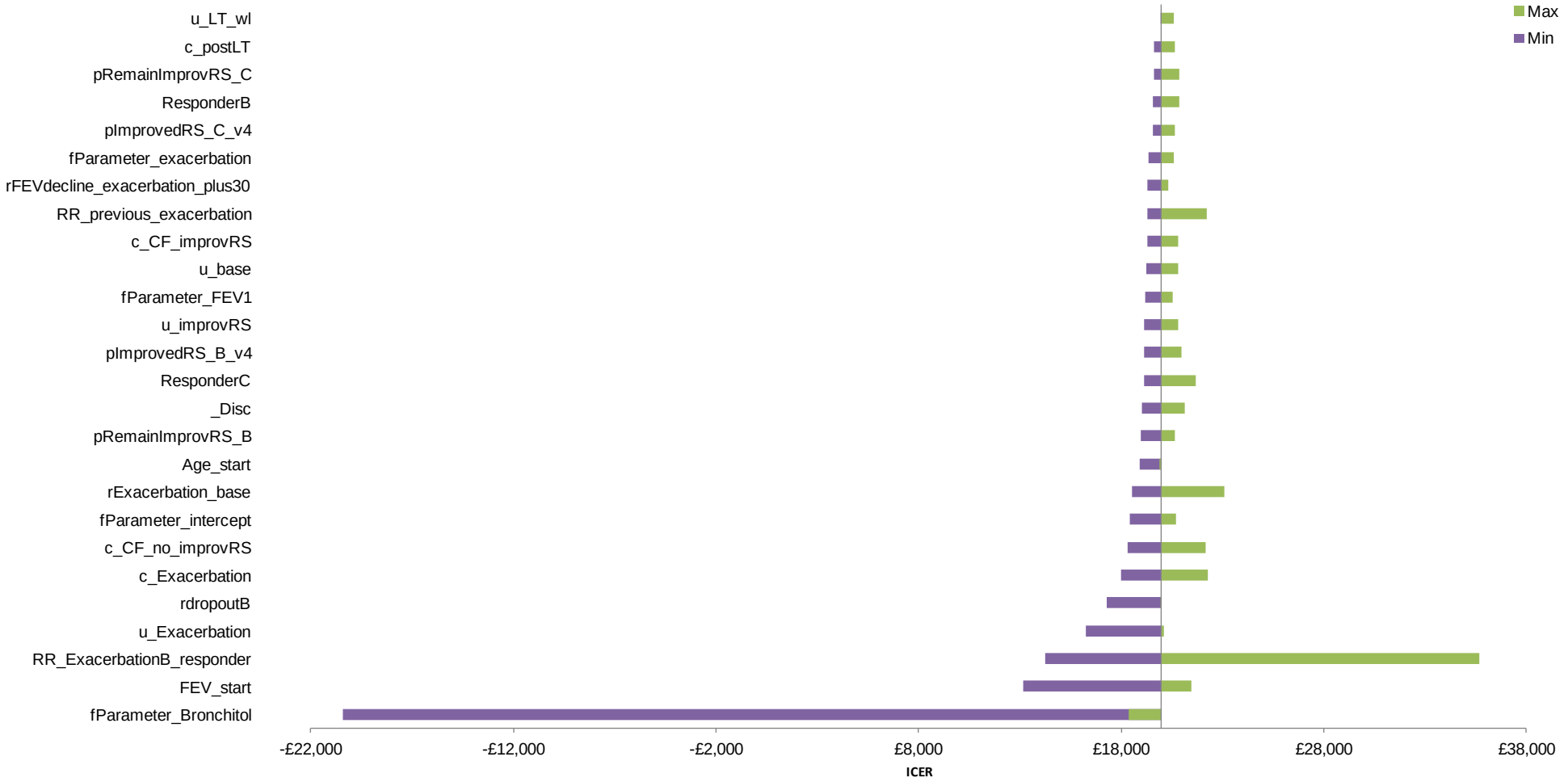
Variable	Min	Max	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Cholesky decomposition method for Exacerbation used to calculate decline in FEV1 % predicted	-3.17	-0.98	10,887	0.56	19,338	10,645	0.52	20,590
Exacerbation								
Baseline annual exacerbation rate	0.50	1.50	11,885	0.51	23,106	10,254	0.55	18,516
Relative risk for patient experiencing an exacerbation over the age of 30	1.22	1.45	10,848	0.55	19,809	10,972	0.54	20,161
Relative risk exacerbation with Bronchitol treatment - treatment responders	0.17	0.91	8,289	0.58	14,277	16,678	0.47	35,685
Relative risk of experiencing an exacerbation if patient has experienced an exacerbation in the previous year.	1.00	1.82	11,545	0.52	22,216	10,660	0.55	19,315
Lung transplant & mortality								
Hazard rate ppFEV1 from survival analysis model used in PI method for mortality	0.94	0.97	12,644	0.64	19,808	7,480	0.37	20,433
Relative risk of death due to a Bcc infection	1.00	10.75	10,768	0.54	19,985	10,875	0.54	20,033
Utility								
Baseline utility score CF patient	0.86	0.93	10,894	0.52	20,787	10,894	0.57	19,238
Utility decrement for exacerbation	-0.33	0.00	10,894	0.67	16,278	10,894	0.54	20,115
Utility patient with improvement in respiratory symptoms	0.85	0.99	10,894	0.52	20,796	10,894	0.57	19,148
Utility no improvement in respiratory symptoms	0.85	0.95	10,894	0.53	20,588	10,894	0.56	19,445
Utility CF patients on LT waiting list (ppFEV<30)	0.24	0.38	10,894	0.55	19,930	10,894	0.53	20,599
Costs								
Cost for the Bronchitol initiation Dose Assessment - BIDA test	8.27	12.41	10,864	0.54	19,993	10,868	0.54	19,999
6-month cost for patients with improved RS	1,661	3,057	10,476	0.54	19,278	11,315	0.54	20,823

Variable	Min	Max	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
6-month cost for patients with no improved RS	1,735	5,247	9,951	0.54	18,312	12,061	0.54	22,194
Cost to treat a pulmonary exacerbation	3,787	8,991	7,882	0.44	17,973	9,780	0.44	22,301
Cost lung transplant	11,054	63,995	10,981	0.54	20,258	10,668	0.54	19,682
Post lung transplant treatment cost	25,152	121,205	11,204	0.54	20,671	10,637	0.54	19,625
Discount rate costs and effects	0.00	0.06	21,530	1.13	19,010	7,650	0.36	21,134

Table 25 Results varying CF mortality

Variable	Bronchitol cost (£)	Bronchitol QALYs	Control cost (£)	Control QALYs	Incremental Cost (£)	Incremental QALY	ICER (£)
CF mortality increased 20%	167,482	9.67	156,915	9.15	10,567	0.52	20,131
CF mortality increased 50%	148,967	8.64	139,124	8.16	9,843	0.48	20,361

Figure 1 Tornado Diagram



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 Bronchitol treatment. This is due to the high uncertainty around this parameter (mean=0.398 95% CI= [0.17; 0.91]). In addition to the risk on pulmonary exacerbations, the detrimental effects of this on a patient's QoL was another important driver.

When looking at the parameters related to lung functioning, the effect of Bronchitol 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]). The decline in lung function after the first 26 weeks has less impact on the ICER.

Of the utilities, the utility decrement for exacerbation had the most impact. Finally the patient's FEV_1 % predicted at baseline has a significant impact on the model, the ICER being lowest in patients with lower FEV_1 % predicted.

The impact of lung transplant rate and its cost is low probably reflecting the only marginal absolute difference in events between the treatment groups.

The cost to treat a pulmonary exacerbation and the background cost of CF for patients without improvement of respiratory symptoms had a large impact on the ICER.

3.3.2 Probabilistic sensitivity analysis

The probabilistic sensitivity analysis comparing Bronchitol to Control provided a mean ICER of £21,801 (95% CI -1,450; 49,686).

Table 26 Results PSA

Statistic	Cost Bronchitol	Cost Control	Δ Cost	QALY Bronchitol	QALY Control	Δ QALY	ICER
Mean	369,526	174,343	10,408	10.56	10.06	0.49	21,801
Median	366,608	172,362	10,409	10.52	10.04	0.49	20,466
SD	60,918	30,998	5,362	0.72	0.80	0.26	29,414
Min	223,233	98,533	-6,810	8.51	7.68	-0.38	-546,816
Max	613,763	299,947	27,742	13.37	13.13	1.42	377,910
2.5% percentile	263,846	120,095	-535	9.29	8.60	-0.06	-1,450
97.5% percentile	499,409	242,389	20,985	12.01	11.76	1.01	49,686

Figure 2 ICER scatter plot

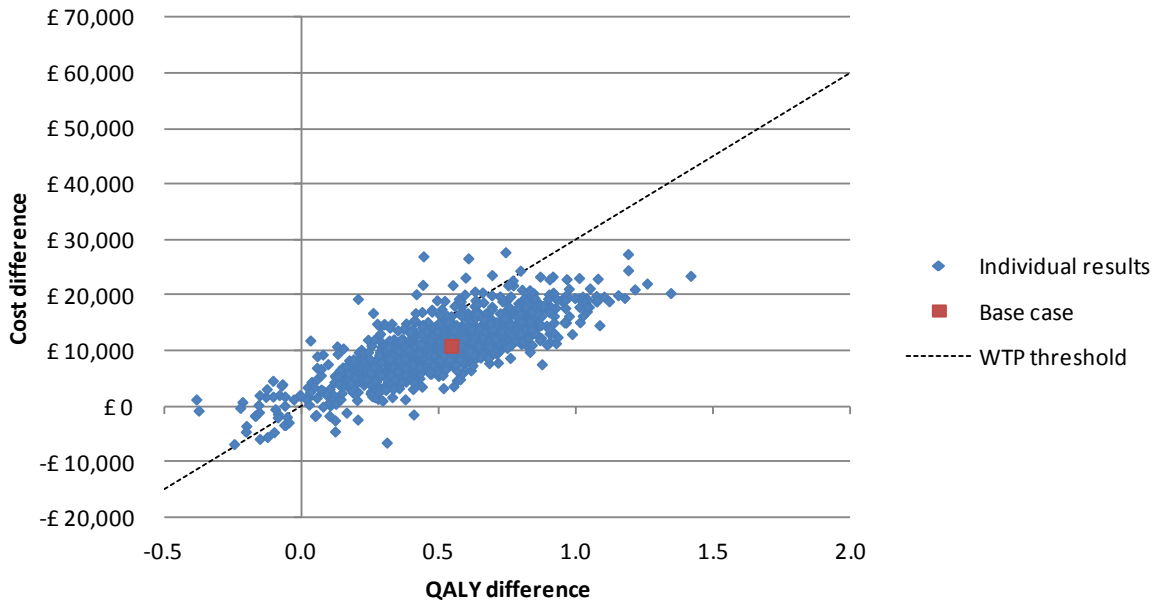


Figure 3 Cost-effectiveness acceptability curve

The results shown in Table 26, Figure 2, and Figure 3 are based on 1,000 samples each containing 10,000 trials. The probability of the ICER being below a WTP threshold of £30,000 was 82.2%. At a WTP threshold of £20,000 these probability was 46.5%, respectively.

3.3.3 Scenario analysis

The updated economic model includes several scenario analyses which are detailed below.

Discontinuation rule

In this scenario 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.

A number of parameters in the model are adjusted to reflect the new responder definition. The list and the values used in this scenario are presented in Table 27 below.

Table 27 Summary of variables applied in the economic model: new responder definition

Variable name	Variable description	Value	Distribution
fParameter_intercept	Parameter estimate of intercept*	-5.348	Multivariate Normal, using Cholesky decomposition
fParameter_BMI	Parameter estimate of BMI*	0.417	Multivariate Normal, using Cholesky decomposition
fParameter_FEV1	Parameter estimate of FEV_1 % predicted at baseline*	0.914	Multivariate Normal, using Cholesky decomposition
fParameter_Bronchitol	Parameter estimate for treatment with Bronchitol*	0.650	Multivariate Normal, using Cholesky decomposition
fParameter_PDPE	Parameter estimate for number of exacerbations used to predict the FEV_1 % predicted after 26 weeks of treatment*	-2.356	Multivariate Normal, using Cholesky decomposition
fParameter_responder	Parameter estimate for response to treatment*	5.890	Multivariate Normal, using Cholesky decomposition
ResponderB	Probability of being a responder to Bronchitol	0.553	Beta n = 85, r = 47
ResponderC	Probability of being a responder to Control	0.367	Beta n = 49, r = 18
RR_ExacerbationB_ responder	Relative risk exacerbation with Bronchitol (patients who respond to treatment)	0.375	Log-Normal u (mean of logs) = -0.981, sigma (std dev of logs) = 0.4475
rdropoutB	Annual drop-out rate for the Bronchitol responders	0.415	Beta alpha = 5.834, beta = 8.216

* Parameter estimate in multivariate regression model for FEV_1 % predicted after 26 weeks

Table 28 Results scenario analysis using a modified responder definition

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Control	170,658	11.21	9.91				
Bronchitol	180,926	11.77	10.44	10,268.39	0.56	0.53	19,550

Pulmonary exacerbation rate

In this scenario the exacerbation rate in the control group is assumed to be 1.5, 2 and 3. The results are presented in Table 29 below.

Table 29 Results scenario analysis using higher exacerbation rate

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Rate=1.5							
Control	199,883	10.66	9.34				
Bronchitol	210,137	11.23	9.89	10,254.47	0.57	0.55	18,516
Rate=2							
Control	220,456	10.22	8.89				
Bronchitol	230,700	10.80	9.46	10,244.23	0.58	0.57	18,023
Rate=3							
Control	247,763	9.72	8.35				
Bronchitol	258,232	10.29	8.92	10,468.52	0.57	0.57	18,396

Varying the exacerbation rate had only a minor impact on the final outcomes.

Maintained treatment benefit and drop-out rate

Three scenarios were run related to treatment benefit and treatment discontinuation. These scenarios were as follows:

- The % predicted FEV_1 at 26 weeks was not carried forward in the model that is, the natural decline of % predicted FEV_1 in patients treated with Bronchitol was assumed to start immediately after 26 weeks. In this scenario all responders continue treatment (no drop-outs)
- The % predicted FEV_1 at 26 weeks was carried forward in the model for 4 cycles (48 weeks) that is, the natural decline of % predicted FEV_1 in patients treated with Bronchitol is assumed to start only immediately after 74 weeks. All responders continue treatment (no drop-out)
- The % predicted FEV_1 at 26 weeks was carried forward in the model for 8 cycles (96 weeks) that is, the natural decline of % predicted FEV_1 in patients treated with

Bronchitol starts only after 122 weeks. In this scenario Bronchitol responders are allowed to discontinue treatment.

Table 30 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 (£) versus baseline (QALYs)
% predicted FEV_1 at 26 weeks not carried forward and no drop-out included							
Control	171,619	11.27	9.96				
Bronchitol	193,634	12.55	11.23	22,014.28	1.28	1.27	17,312
% predicted FEV_1 at 26 weeks carried forward for 4 cycles and no drop-out inlcuded							
Control	171,619	11.27	9.96				
Bronchitol	194,637	12.62	11.29	23,017.85	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				
Bronchitol	182,981	11.87	10.53	11,361.84	0.60	0.57	19,844

Shorter time horizon

In this scenario the impact of a shorter time horizon as a proxy for a shorter duration of effectiveness of Bronchitol (i.e. shorter than life time) was assessed.

Table 31 Results varying time horizon

Variable	Bronchitol cost (£)	Bronchitol 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

The ICER is sensitive to the time horizon and increased with shorter time horizon being £45,329 per QALY gained for 5 years and £25,151 per QALY gained for 10 years.

3.4 Conclusion

The economic model developed, evaluated the costs and outcomes of using Bronchitol in adult CF patients receiving Best Supportive Care (BSC) without rhDNase use.

The analysis shows that in adult rhDNase non-users, adding Bronchitol to BSC is cost-effective with an ICER of £19,993/QALY. In the PSA, the probability of the ICER being below a WTP threshold of £30,000 was 82.2%, and in lowering the WTP threshold to £20,000, the

probability was 46.5%, both of which represent reasonable levels of cost-effectiveness on a population basis. In sensitivity analysis, the results remained robust, with greatest variance on the ICER result being the treatment effect associate with Bronchitol. Since the base case has taken a conservative approach wherever choices have needed to be made, the result of this variation was generally to reduce the ICER results.

Consistent with the clinical unmet needs of the CF community in England Wales, Bronchitol represents a cost-effective option for patients receiving Best Supportive Care, without add-on rhDNase

4 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
- FEV_1 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 0% rule(1=Yes / 0=No)= FEV1PR0_2
- Responder 5% rule(1=Yes / 0=No)= scen1

* 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

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 32 for the continuous variables.

Table 32. 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 33.

Table 33. FEV_1 % 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				0.4716

Variable	N	Mean[SD]	95% CI	p-value
Not improved	76	63.16 [15.009]	[59.728; 66.587]	
Improved	50	65.15 [15.343]	[60.788; 69.509]	
Vitality				0.0823
Not improved	101	62.78 [15.623]	[59.700; 65.868]	
Improved	25	68.65 [11.995]	[63.698; 73.600]	
Physical symptoms				0.7271
Not improved	105	64.16 [15.199]	[61.218; 67.100]	
Improved	21	62.89 [14.995]	[56.065; 69.717]	
Responder 0% rule				0.0220
Non-responder	40	59.45 [16.615]	[54.134; 64.762]	
Responder	86	66.04 [13.973]	[63.045; 69.037]	
Responder 5% rule				0.0377
Non-responder	61	61.07 [15.908]	[56.994; 65.142]	
Responder	65	66.65 [13.912]	[63.203; 70.097]	

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.

The following variables were included in the multivariate model:

Quantitative:

- Age at baseline (continuous)=age
- BMI at visit 1 (continuous)= BMI_v1
- FEV_1 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 0% rule(1=Yes / 0=No)= FEV1PR0_2
- Responder 5% rule(1=Yes / 0=No)= scen1

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

Based on the definition of the responder at week 6, two models were considered.

4.2.1 Model 1: responder definition of 0%

Five steps were necessary to obtain the final model. 126 observations had been used from the 134 in total. The final model includes treatment group, FEV_1 percentage predicted at visit 1, and being a responder. The parameter estimates, p-values and the variance inflation factor are given in Table 34 below.

All predictors in the model except treatment group are significant at level 0.05, and adjusted R-square of the model is 0.797 which means 79.7% 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 34. Model 1 for FEV_1 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	0.67561	2.93364	0.23	0.8182	0
Treatment group(1=Mannitol/ 0=Control)	1	1.12080	1.28222	0.87	0.3838	1.06078
% predicted FEV_1 (Imputed) at V1	1	0.93068	0.04337	21.46	<.0001	1.00704
Relative change from Baseline in % predicted FEV_1 (imputed) at V2 >0 (0=Non-Resp; 1=Resp)	1	6.67049	1.33887	4.98	<.0001	1.05451

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 4. Histogram of the residuals for Model 1- ADULTS rhDNase non-users

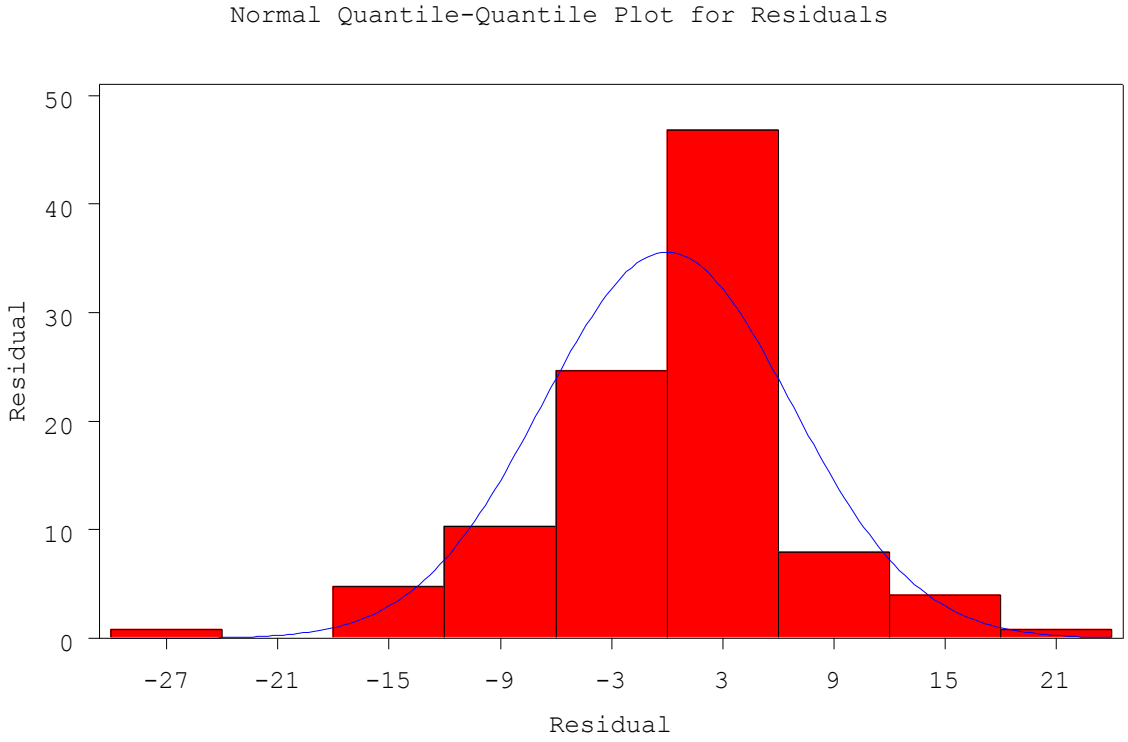
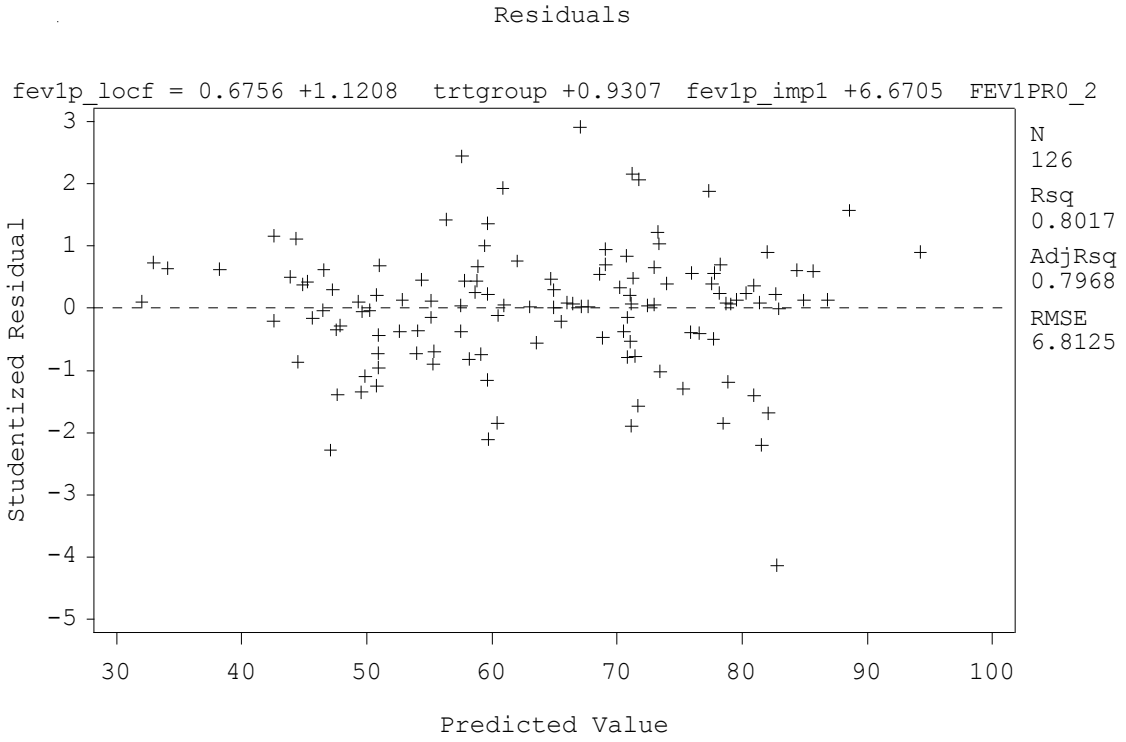
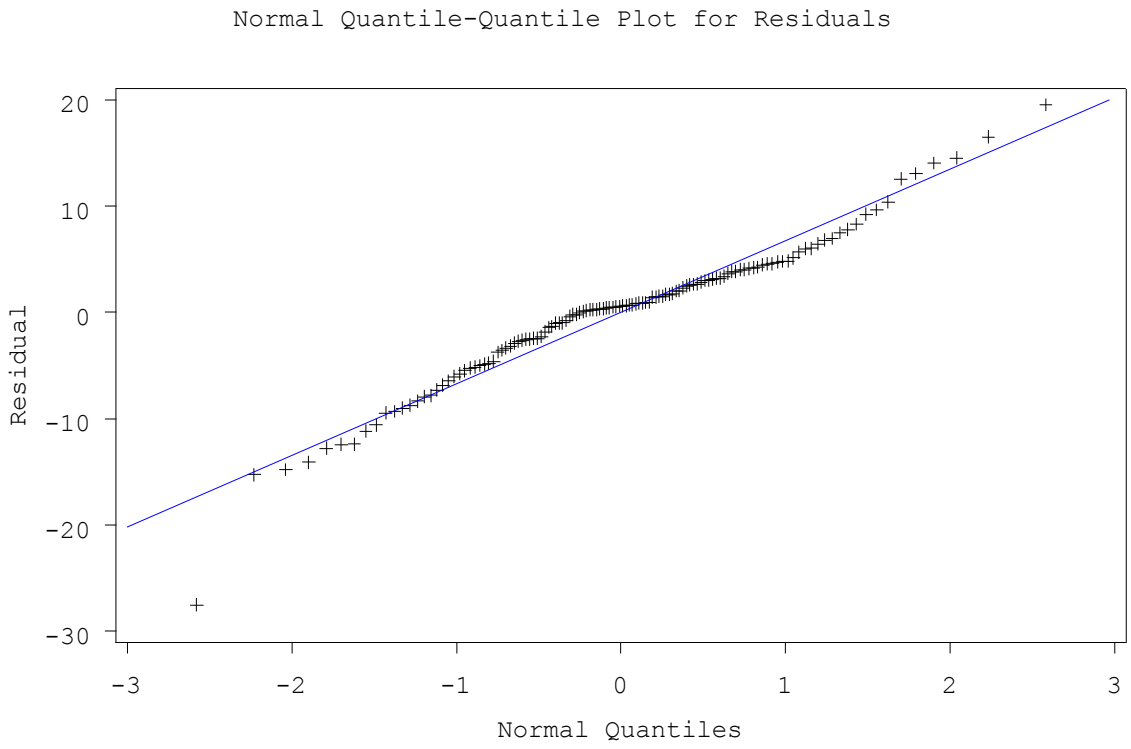


Table 35. Covariance matrix for Model 1 for FEV_1 percentage predicted at visit 4 allowing for growth – Adults rhDNase non-users

Variable	Intercept	trtgroup	fev1p_imp1	FEV1PR0_2
Intercept	8.6062479434	-0.451755224	-0.115683833	-1.096161447
Treatment group(1=Mannitol/0=Control)	-0.451755224	1.6440883675	-0.004601423	-0.389773282
% predicted FEV_1 (Imputed) at V1	-0.115683833	-0.004601423	0.0018808305	0.0017777375
Relative change from Baseline in % predicted FEV_1 (imputed) at V2 >0 (0=Non-Resp; 1=Resp)	-1.096161447	-0.389773282	0.0017777375	1.7925731931

Figure 5. Residual plots for Model 1- Adults rhDNase non-users





4.2.2 Model 2: responder definition of 5%

Seven steps were necessary to obtain the final model. 126 observations had been used from the 134 in total. The final model includes treatment group, FEV_1 percentage predicted at visit 1, and being a responder. The parameter estimates, p-values and the variance inflation factor are given in Table 36 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 36. Model 2 for FEV_1 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	-5.34839	4.59156	-1.16	0.2464	0
Treatment group(1=Mannitol/0=Control)	1	0.65007	1.24125	0.52	0.6014	1.07547
BMI (kg/m²) at V1	1	0.41700	0.17511	2.38	0.0188	1.02365
% predicted FEV_1 (Imputed) at V1	1	0.91411	0.04243	21.54	<.0001	1.04310
Number of PDPE in DBP	1	-2.35608	1.11116	-2.12	0.0360	1.05991
Responder for scenario 1	1	5.88975	1.22498	4.81	<.0001	1.10077

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

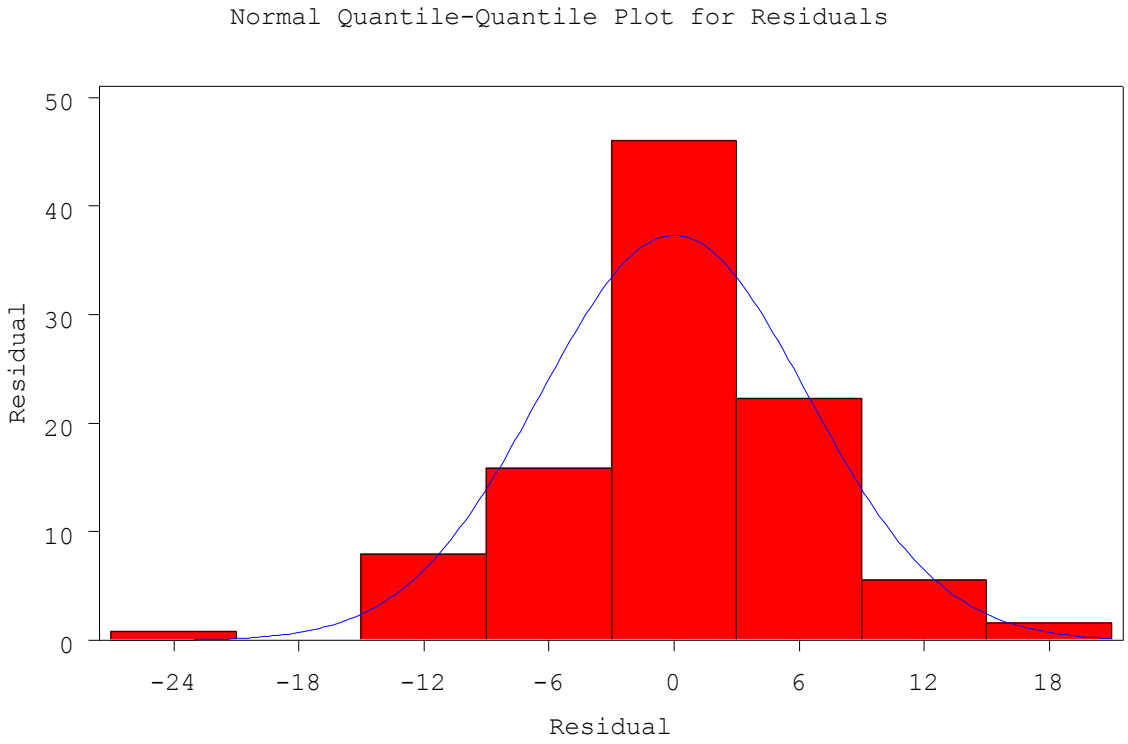
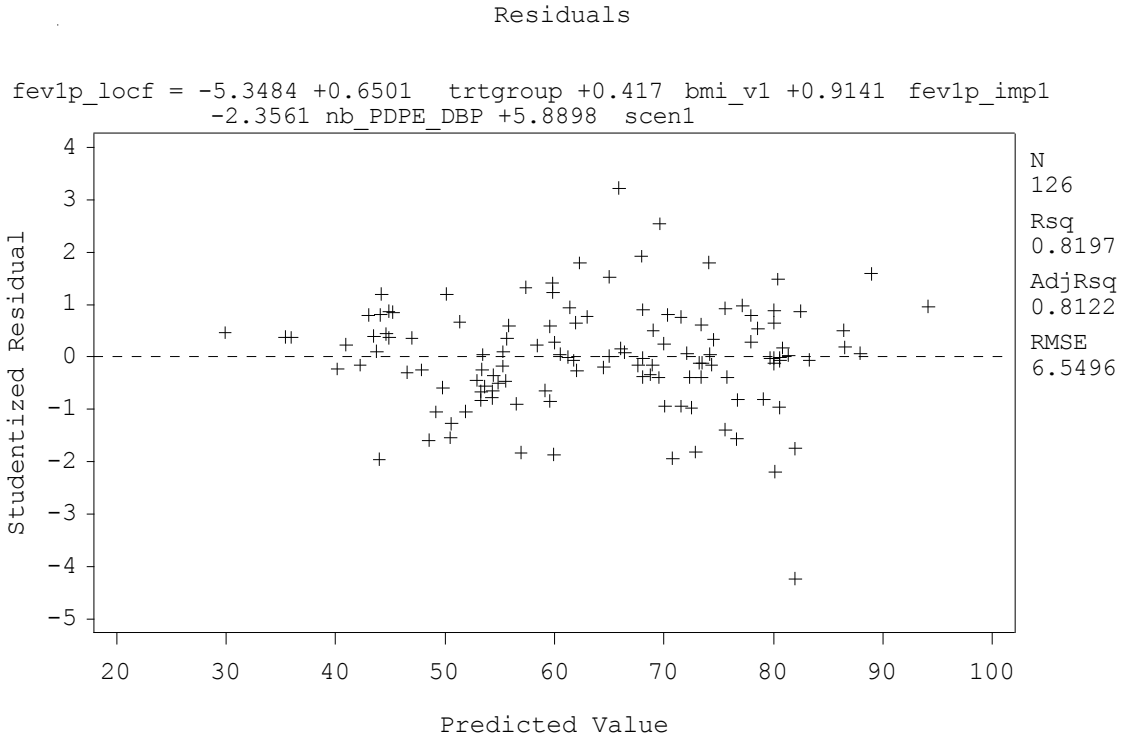
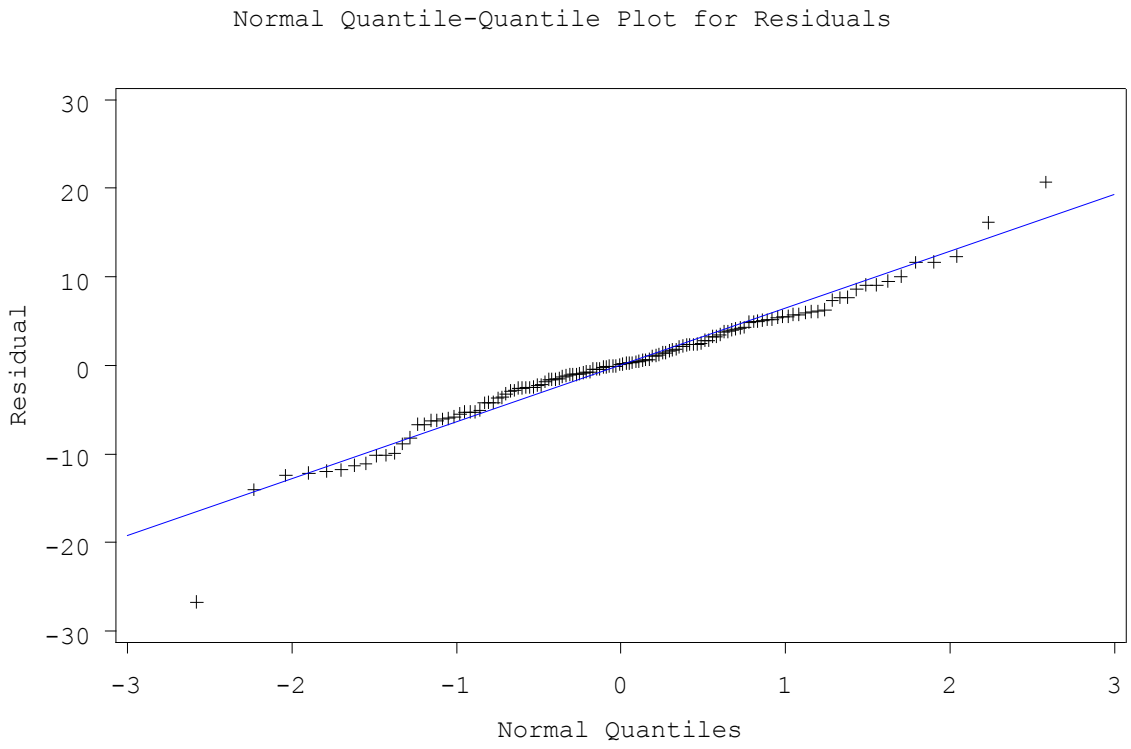


Table 37. Covariance matrix for Model 2 for FEV_1 percentage predicted at visit 4 allowing for growth – Adults rhDNase non-users

Variable	Intercept	trtgroup	bmi_v1	fev1p_imp1	nb_PDPE_DBP	scen1
Intercept	21.08243	-0.27423	-0.62588	-0.09188	-0.81733	-0.72378
Treatment group(1=Mannitol/0=Control)	-0.27423	1.54069	-0.01191	-0.00391	0.08451	-0.33967
BMI (kg/m²) at V1	-0.62588	-0.01191	0.03067	-0.00096	-0.00253	-0.00842
% predicted FEV_1 (Imputed) at V1	-0.09188	-0.00391	-0.00096	0.00180	0.00584	0.00454
Number of PDPE in DBP	-0.81733	0.08451	-0.00253	0.00584	1.23468	0.24471
Responder for scenario 1	-0.72378	-0.33967	-0.00842	0.00454	0.24471	1.50057

Figure 7. Residual plots for Model 2- Adults rhDNase non-users





[1] Bradley J, Blume S, Balp M, Elborn S. Incidence and resource utilisation of pulmonary exacerbations in patients with cystic fibrosis in the UK. Presented at European Respiratory Society (ERS) Annual Congress, 2010 18-22 Sep;Barcelona, Spain. 2010.
[2] Jarad NA, Giles K. Risk factors for increased need for intravenous antibiotics for pulmonary exacerbations in adult patients with cystic fibrosis. *Chron Respir Dis* 2008;5(1):29-33

The use of airway clearance drugs in UK adult CF patients

Results of an internet based survey – June 2012

Key messages

- To be able to provide an insight to NICE of the current treatment practices for adult CF patients in the UK, an independently conducted survey was commissioned by Pharmaxis (June 2012). Specifically, the survey examined rhDNase and hyprertonic saline usage; treatment satisfaction; and how expert CF physicians would use Bronchitol based on their current case mix.
- Although some respondents took up their right to complete anonymity and did not provide the details of the expert centre they worked at, the survey covered at least 10 out of the 19 Adult CF centres in England and Wales and contains the opinions of 29 clinicians that treat more than 80% of all adult patients within the UK (see Participants section below).
- The results of the survey clearly demonstrate that most patients in UK CF adult centres have already been trialled on the existing airway clearance drugs. According to clinicians' responses, only 18% of patients have never used rhDNase or hypertonic saline and consequently the opportunity for Bronchitol to be used as a first line agent is very small.
- Hypertonic saline usage is fairly common in CF adults, but its usage at a dose that has been proven to reduce exacerbations in a randomised controlled trial (7% BD) is low. No qualitative information was collected in the survey to find out why hypertonic saline is chronically under dosed but the comments from the clinician and patient during the first NICE appraisal meeting suggest that poor tolerability is a key factor.
- About one third of patients are perceived by clinicians to be uncontrolled irrespective of the treatment they are taking. This underlines the level of unmet need which exists in the adult CF population despite the widespread use of existing treatments
- Clinicians see Bronchitol as a potentially useful treatment option, particularly in patients who are not well controlled despite treatment with hypertonic saline and/or rhDNase (50% of the proposed population), and a beneficial option for patients not currently receiving treatment (19%).
- Extrapolating these results to the CF population in the UK, the proposed Bronchitol-treated population would be 1,000 patients (Based on BIDA and responder stopping rules at 6 weeks, the actual number of eligible patients that would continue to receive treatment over the longer term would be lower). This compares with the 4,000 patients currently estimated to be on rhDNase and the 3,600 patients estimated to be on hypertonic saline.
- Bronchitol was not perceived as a treatment that will replace existing treatments on a significant scale when those patients are well controlled.
- The % of patients on hypertonic saline who are well controlled that would be considered for a trial on Bronchitol is very low (11%).

Research methodology

Confidential on line survey conducted to Industry codes of conduct

An independently conducted on-line survey of practicing CF clinicians in adult CF centres in England and Wales was commissioned by Pharmaxis (see Appendix I). It was conducted by First Line Research (York, UK) in June 2012 and was carried out within the codes of conduct of the Market Research Society and the British Healthcare Business Intelligence Association. The internet based questionnaire took about 10 minutes to complete for each respondent and the identity of both the respondents and their Centres were not disclosed to Pharmaxis.

Participants

Data collected on more than 80% of UK adult CF patients

29 CF respiratory physicians responded to the survey. Although some respondents took up their right to complete anonymity and did not provide the details of the expert centre they worked at, the survey covered at least 10 out of the 19 Adult CF centres in England and Wales. Within these 29 responders were 18 Consultant Physicians and 11 Senior Registrars. Together they reported that they were responsible for 4,147 patients of which 4,002 were adults. This represents more than 80% of all adult patients within the UK, although it is important to note that this is based on the feedback of the interviewees and not on a formal audit. [UK CF Trust registry 2010 records 9,385 CF patients and of the 7,937 with complete data, 55% of them were aged 16 or above]

Research Scope

Focussed on collecting airway clearance treatment history and practice

Respondents were requested to review the adult (18+) patients they were currently responsible for and provide information on the use of airway clearance drugs; rhDNase and hypertonic saline. They were asked to assess the history of usage of these drugs in their patients, how the drugs were currently used and how well their patients were currently doing on the drugs. Participants were then shown a profile of Bronchitol (see Appendix II) which matches that presented in the manufacturer's NICE submission, and respondents were asked what % of patients they thought Bronchitol would be trialled in. A patient flow was derived from the results (see Appendix III).

Results

1. Historical use of airway clearance drugs

Treatment	HS of any strength	HS > 6% alone	rhDNase alone	HS 6%+ and rhDNase	Never used HS 6% + or rhDNase
% ever used	57%	37%	58%	28%	18%

This demonstrates clearly that most patients in UK CF adult centres have already been trialled on the existing airway clearance drugs. Only 18% of patients have never used rhDNase or hypertonic saline and consequently the opportunity for Bronchitol to be used as a first line agent is very small.

2. Current use of airway clearance drugs

Treatment	HS of any strength	HS 6%+ alone	HS 6%+ BD alone	rhDNase alone	HS 6%+ and rhDNase
% currently using	41%	25%	17%	43%	22%

There is no CF Trust registry data on hypertonic saline use to compare with the survey results but the 65% of patients (18+) recorded here as taking rhDNase either alone or in combination with HS appears slightly over reported compared with the 51% of patients aged 16 and above recorded as taking rhDNase in the 2010 CF Trust Registry. It should be noted that rhDNase use is only available for 85% of the patients in the registry.

The other notable finding in the survey is that whilst hypertonic saline usage is fairly common in CF adults, its usage at a dose that has been proven to reduce exacerbations in a randomised controlled trial (7% BD) is much lower. No qualitative information was collected in the survey to find out why hypertonic saline is chronically under dosed but the comments from the clinician and patient during the first NICE appraisal meeting suggest that poor tolerability is a key factor.

3. Level of unmet need

Treatment	HS 6%+ BD alone		rhDNase alone		HS 6%+ and rhDNase	
% currently using	17%		43%		22%	
% controlled / uncontrolled	65%	35%	67%	33%	70%	30%

In each of these treatment groups about one third of patients are perceived by clinicians to be uncontrolled. This underlines the level of unmet need which exists in the adult CF population despite the widespread use of existing treatments.

4. The place for Bronchitol

Treatment	HS 6%+ BD alone		rhDNase alone		HS 6%+ and rhDNase		No Treatment
% currently using	17%		43%		22%		18%
% controlled / uncontrolled	65%	35%	67%	33%	70%	30%	n/a
% considered for Bronchitol trial	11%	37%	11%	41%	16%	47%	23%
Patient numbers considered for Bronchitol trial[1]	48	86	128	238	97	123	167

[1] *Number of patients out of the 4,002 covered by the survey. These were calculated by scaling the patient numbers reported in the survey as being controlled or uncontrolled by a factor of 29 and then multiplying that number by the % reported as suitable for trial.*

In this survey of 29 clinicians responsible for treating 4,002 adult CF patients the total number of patients they think would be suitable to trial Bronchitol in is 888. 447 of these are currently uncontrolled, 274 are controlled and 167 not on any treatment. Taking into account the total number of adult CF patients in the UK including those not covered by the survey then the number

would rise to approximately 1,000. This compares with the 4,000 patients currently estimated to be on rhDNase (ref CF Trust registry and IMS data) and the 3,600 patients estimated to be on hypertonic saline in the survey.

These results confirm that clinicians see Bronchitol as a useful treatment particularly in patients who are not well controlled despite treatment with hypertonic saline and/or rhDNase; 42% of uncontrolled patients were deemed suitable for trial with Bronchitol. It is not perceived as a treatment that will replace existing treatments on a significant scale when those patients are well controlled; only 11% of controlled patients were deemed suitable for trial with Bronchitol. In particular the % of patients on hypertonic saline who are well controlled that would be considered for a trial on Bronchitol is very low (11%).

Appendix I – Study Questionnaire

Terms

This study is being conducted on behalf of a pharmaceutical company to understand aspects of your treatment of Cystic Fibrosis (CF) patients.

Please review the following:

❍ The survey should take approximately 10 minutes to complete

❍ I understand that the aim of this research is to gain my views for market research purposes only and is not intended to be promotional

❍ I understand that this research is sponsored by a pharmaceutical company and is being carried out within the codes of conduct of the Market Research Society and the British Healthcare Business Intelligence Association

❍ I agree that anything I see or read during this research should be treated as confidential

❍ I understand that the identity of respondents is confidential and none of my details will be passed on to any 3rd party

❍ I understand that any information I disclose will be treated in the strictest confidence and the results of the research aggregated to provide an overall picture of attitudes to the areas being covered in this survey. No answers will be attributable to me as an individual

❍ I have the right to withdraw from the survey at any time and to withhold information as I see fit

❍ Any stimulus materials shown during the course of this market research interview are for exploratory purposes only. Some of the information shown in the materials may be hypothetical, and you should not use the information presented for any purpose other than to answer the market research questions posed

We are required to pass on to our client details of adverse events that are mentioned during the course of market research. Although what you say will, of course, be treated in confidence, should you raise during the discussion an adverse event in a specific patient or group of patients, we will need to report this even if it has already been reported by you directly to the company or the relevant regulatory authorities. In such a situation you will be asked whether or not you are willing to waive the confidentiality given to you under the market research Codes of Conduct specifically in relation to that adverse event. Everything else you say during the course of the interview will continue to remain confidential, and you will still have the option to remain anonymous if you so wish.

Please confirm that you have read, understood and accept the points above and are happy to proceed with the market research survey on this basis.

❍ Yes (1)
❍ No (2)

s1

Are you a secondary care / hospital doctor currently treating respiratory disease in patients suffering from cystic fibrosis?

❍ Yes (1)
❍ No (2)

s2

Please confirm your current grade:

❍ Consultant (1)
❍ Specialist Registrar / Senior Registrar (2)
❍ Other (3)

s3

Please type in your current job title:

NB – this will be kept confidential and used only for classification purposes.

_____

s4

In total, approximately how many cystic fibrosis patients are currently registered as being under your care?

_____ patients (1)

s5

And approximately how do those [s4_(1)] cystic fibrosis patients break down across the following groups?

Please ensure your answers here sum to exactly [s4]

_____ adult patients (age 18+) (1)

_____ paediatric patients (2)

q1

Thinking about all of your current [s5_(1)] adult cystic fibrosis patients, what percentage...

Your answers here may, or may not, sum to 100% i.e. some patients may fall into more than one category.

...have ever received hypertonic saline of any strength? _____ % (1)

...have ever received hypertonic saline of at least 6% strength (alone)? _____ % (2)

...have ever received Pulmozyme (alone)? _____ % (3)

...have ever received hypertonic saline of at least 6% strength and Pulmozyme together? _____ % (4)

...have NEVER received either hypertonic saline (of at least 6% _____ % (5)

strength) or Pulmozyme?

If q1_(1) > 0 OR q1_(2) > 0 ask q2a

q2a

Thinking again about all of your current [s5_(1)] adult cystic fibrosis patients, what percentage...

...are currently receiving hypertonic saline of any strength? _____ % (1)

...are currently receiving hypertonic saline of at least 6% strength (alone)? _____ % (2)

If q2a_(1) > 0 ask q2b

q2b

Thinking about current adult cystic fibrosis patients currently receiving hypertonic saline of at least 6% strength (alone), what percentage of these patients are taking it twice daily?

_____ % (1)

If q2b_(1) > 0 ask q2c

q2c

And amongst adult cystic fibrosis patients currently receiving hypertonic saline of at least 6% strength (alone) twice daily, what percentage are...

Please ensure your answers sum to exactly 100.

...controlled? _____ % (1)

...inadequately controlled? _____ % (2)

If q1_(3) > 0 ask q3a

q3a

Thinking again about all of your current [s5_(1)] adult cystic fibrosis patients what percentage are currently receiving Pulmozyme (alone)?

_____ % (1)

If q3a_(1) > 0 ask q3b

q3b

And amongst adult cystic fibrosis patients currently receiving Pulmozyme (alone), what percentage are...

Please ensure your answers sum to exactly 100.

...controlled? _____ % (1)

...inadequately controlled? _____ % (2)

If q1_(3) > 0 ask q3c

q3c

Thinking now about adult cystic fibrosis patients who in the past received Pulmozyme (alone) but no longer do so, for what reasons is Pulmozyme typically stopped?

Please select as many as apply and/or type in other reasons

- ❑ Inadequate control (1)
- ❑ No perceived benefit (2)
- ❑ Patient choice (3)
- ❑ Adverse reactions (4)
- ❑ Didn't meet formulary continuation criteria (5)
- ❑ Other reason, please specify (6)_____
- ❑ Other reason, please specify (7)_____

If q1_(4) > 0 ask q4a

q4a

Thinking again about all of your current [s5_(1)] adult cystic fibrosis patients what percentage are currently receiving hypertonic saline (of at least 6% strength) and Pulmozyme together?

_____ % (1)

If q4a_(1) > 0 ask q4b

q4b

And amongst adult cystic fibrosis patients currently receiving hypertonic saline (of at least 6% strength) and Pulmozyme together, what percentage are...

Please ensure your answers sum to exactly 100.

...controlled? _____ % (1)

...inadequately controlled? _____ % (2)

iNice

Please now review the information below:

[Bronchitol profile appears here]

We are interested in the types of cystic fibrosis patients, if any, where you think you would be likely to consider a trial on Bronchitol, and about how many of these patients there are likely to be.

Patient groups shown in q5a answer list correspond to patient groups with > 0 patients (previous questions)

q5a

Thinking about the following groups of adult cystic fibrosis patients, what percentage of patients in each group – if any – would you consider for a trial on Bronchitol?

Click here to review the Bronchitol profile.

Patients currently receiving hypertonic saline of at least 6% strength (alone) twice daily and are adequately controlled _____ % (1)

Patients currently receiving Pulmozyme (alone) and are adequately controlled _____ % (2)

Patients currently receiving hypertonic saline (of at least 6% strength?) and Pulmozyme together and are adequately controlled _____ % (3)

Patients currently receiving hypertonic saline of at least 6% strength (alone) twice daily and are not adequately controlled _____ % (4)

Patients currently receiving Pulmozyme (alone) and are not adequately controlled _____ % (5)

Patients currently receiving hypertonic saline (of at least 6% strength) and Pulmozyme together and are not adequately controlled _____ % (6)

If q1_(5) > 0 ask q5b

q5b

Thinking about adult cystic fibrosis patients currently receiving NEITHER hypertonic saline (of at least 6% strength) or Pulmozyme, how might such patients now be treated?

Please ensure your answers sum to exactly 100.
Click here to review the Bronchitol profile.

No treatment _____ % (1)

Considered for a trial on Bronchitol _____ % (2)

Receive hypertonic saline of at least 6% strength (alone) twice daily? _____ % (3)

Receive Pulmozyme (alone) _____ % (4)

Receive hypertonic saline (of at least 6% strength?) and Pulmozyme together _____ % (5)

Other treatment option/s _____ % (6)

If q1_(3) > 0 ask q6

q6

Thinking again about adult cystic fibrosis patients who in the past received Pulmozyme, but no longer do so (either alone or in combination with hypertonic saline of at least 6% strength), what percentage would you now ...

Click here to review the Bronchitol profile.

...re-consider for Pulmozyme treatment? _____ % (1)

...consider for a trial on Bronchitol? _____ % (2)

q7

In your hospital is there currently an agreed stopping rule in place regarding the usage of Pulmozyme?

For example, is treatment routinely discontinued if certain predefined criteria (e.g.FEV1 improvement) are not achieved after a certain period of time?

❍ Yes (1)
❍ No (2)

d1

Thank you. To finish, please can you help us with a few demographic / classification questions...

Please select your region from the list below:

❍ England (North East) (1)
❍ England (North West) (2)
❍ England (Yorkshire and the Humber) (3)
❍ England (East Midlands) (4)
❍ England (West Midlands) (5)
❍ England (East of England) (6)
❍ England (London) (7)
❍ England (South Central) (8)
❍ England (South East Coast) (9)
❍ England (South West) (10)
❍ Wales (11)
❍ Scotland (12)
❍ Northern Ireland (13)

d2

Please confirm your gender:

❍ Male (1)
❍ Female (2)

d3

In what year did you qualify?

Drop down (2012 – Before 1950)

d4

Please confirm the name of your centre / hospital:

NB – this will be kept confidential and used only for classification purposes.

(1) _____

dec

Finally, we may need to declare any conflict of interest amongst those who have assisted in this survey. Do you have a conflict of interest to declare?

❍ Yes (please state) (1)_____
❍ No (2)

Appendix II – Bronchitol product profile

Introduction

Bronchitol (Dry powder mannitol) is an osmotic agent, derived from the sugar-alcohol mannitol, which is manufactured as a respirable dry powder and taken via a portable capsule inhaler.

Bronchitol works by improving airway clearance of mucus build-up commonly found in the lungs of Cystic Fibrosis patients.

Indication

Bronchitol is indicated for the treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to best standard of care.

Key efficacy data

Two double-blind, placebo-controlled Phase III (CF301 and CF302) studies involving over 600 patients have recently been concluded in centres across North and South America, Europe and Australasia. A very wide range of patients, in terms of age (6 years upwards) and severity of disease (FEV_1 between 30-90% of predicted value), were included in the studies. Patients were able to continue all other current therapies, with the exception of hypertonic saline. Over 60% were taking Pulmozyme and over 75% taking TOBI or other inhaled antibiotics.

When the data from these two studies is pooled, a total of 341 adult patients (≥18 yrs) received either Bronchitol 400 mg or control (Bronchitol 50 mg) bid for 26 weeks. Adult treatment and control groups were well matched at baseline for age (mean 28.5 yrs), BMI (22.4 kg/m2), gender (57% male), FEV1 (2.27L), concurrent rhDNase use (61%), nebulised antibiotic use (57%) and *P. Aeruginosa* (65%).

Mean change in FEV1 (mL) from baseline for Bronchitol versus control was statistically significant (99.50 mL $p<0.001$) over 26 weeks of treatment. Overall treatment effect on FVC also favoured Bronchitol over control (128.32 mL $p<0.001$). Exacerbation incidence reduced by 24% (RR 0.76, 95% CI 0.51 to 1.13) compared to control. Importantly, Bronchitol did not increase treatment burden assessed by CFQ-R.

Significant differences in sputum weights between groups were seen at all time points with the higher sputum weights in the Bronchitol group, consistent with the higher increased MCC seen with Bronchitol (7gms, $p<0.0001$).

Safety

In both Phase III trials, there were a similar number of adverse events (AEs) in the active and placebo groups, and no deaths. AEs were generally consistent with those expected in CF.

Respiratory AEs that were more common with Bronchitol compared with placebo included cough (20.2% vs.16.7%), haemoptysis (9.4% vs. 5.4%) and pharyngolaryngeal pain (11.9% vs. 7.5%). Inducing a productive cough at the time of dosing is one of the mechanisms of action of Bronchitol to help clear mucus.

Dosage and administration

Dosage is 10 x 40mg capsules, twice a day, given via a dry powder inhaler.

The average time patients need to take the full dose has been measured at less than 5 minutes in clinical studies.

Appendix III – Patient Flow derived from market research