

Selection of Study Population

A subject was enrolled into the study only if they met all inclusion criteria and none of the exclusion criteria.

In addition, the MTT was utilised to identify and exclude subjects with airway hyperresponsiveness to a test dose of inhaled mannitol. A fall in $FEV_1 < 20\%$ following inhalation of 400 mg mannitol was deemed to be a passing MTT result. Subjects who passed preliminary screening at Visits 0A and 0B were to undergo mannitol tolerance testing at Visit 0B. Passing this test was a prerequisite for randomisation. (See more detail of MTT below)

Slight changes to study inclusion and exclusion criteria were made during the course of the study with an amendment to the original approved version of the protocol (from protocol version 3.0, 13 Aug 2009 to protocol version 5.0, 28 July 2010). Inclusion and exclusion criteria are listed below according to the final approved version of the protocol (protocol version 5.0).

Inclusion Criteria

Subjects were permitted to be included in the study when all of the following criteria were met. The subject must:

1. Have given written informed consent to participate in this study in accordance with local regulations
2. Have documented evidence of confirmed diagnosis of (non-cystic fibrosis) bronchiectasis by CT, HRCT or bronchogram
3. Be aged 18 – 85 years inclusive, male and female.)
4. Have $FEV_1 \geq 40\%$ and $\leq 85\%$ predicted* and $\geq 1.0L$ (*according to NHANESIII 1999 predicted tables) measured at V0A.
5. Clinician documented history of at least two pulmonary exacerbations, each requiring antibiotic therapy, in the last 12 months prior to Visit 0A and a total of at least four in the last two years prior to Visit 0A
6. Have a total SGRQ score of ≥ 30 at Visit 0B
7. Have a production of $\geq 10g$ of sputum at Visit 0B.
8. Have reported chronic sputum production of ≥ 1 tablespoonful (15mL) per day on the majority of days in the 3 months prior to Visit 0A
9. Be able to perform all the techniques necessary to measure lung function
10. Have $FEV_1 \geq 40\%$ predicted* and $\geq 1.0L$ (*according to NHANESIII 1999 predicted tables) measured at V0B (Baseline result prior to MTT administration).

Exclusion Criteria

Subjects were to be excluded from this study if one or more of the following criteria were 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. Have bronchiectasis as a consequence of cystic fibrosis or focal endobronchial lesion or otherwise curable causes (e.g. foreign body aspiration)
3. Be considered “terminally ill” or listed for transplantation
4. Be using hypertonic saline in the 14 days prior to commencing Visit 0B or thereafter at any time during the study.
5. Have previously used inhaled mannitol (Bronchitol) for more than a day
6. Have had a significant episode of haemoptysis (>60 mL) in the previous 6 months
7. Have had rescue antibiotics in the four weeks prior to V0B (chronic background antibiotic therapy accepted)
8. Have smoked within the last three months and must not smoke during their participation in the study
9. Have had a myocardial infarction in the three months prior to Visit 0A
10. Have had a cerebral vascular accident in the three months prior to Visit 0A
11. Have had major ocular surgery in the three months prior to Visit 0A
12. Have had major abdominal, chest or brain surgery in the three months prior to Visit 0A
13. Have a known cerebral, aortic or abdominal aneurysm
14. Have actively treated Mycobacterium tuberculosis
15. Have actively treated or unstable nontuberculous mycobacterial (NTM) infection or be under consideration for NTM treatment in the next 12 months
16. Have unstable ABPA requiring steroid therapy (≤ 5 mg dose oral steroids in stable ABPA accepted)
17. Have end stage interstitial lung disease
18. Have active malignancy including melanoma (other skin carcinomas exempted). Remissions from any malignancy > 2 years also exempted
19. Be breast feeding or pregnant, or plan to become pregnant while in the study
20. Be using an unreliable form of contraception (female subjects at risk of pregnancy only)
21. Be participating in another investigational drug study, parallel to, or within 4 weeks of Visit 0A
22. Have a known intolerance to mannitol or $\beta 2$ -agonists
23. Have uncontrolled hypertension – e.g. for adults: systolic BP > 190 and or diastolic BP > 100
24. Subject has a condition or is 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 subject’s participation in the study
25. Have previously been screen failed for the study. (Exceptions: subjects who previously failed inclusion criteria 3, 4 or 7 or exclusion criteria 5, of previous protocol (protocol version 3.0) were permitted to be rescreened into protocol version 5.0.)

Mannitol Tolerance Test (MTT)

The mannitol tolerance test (MTT) was administered according to a test procedure, prior to randomisation at Visit 0B. The MTT procedure was used to identify subjects with airway hyperresponsiveness in response to inhaled mannitol. This was determined by measuring the degree of bronchoconstriction which occurred following sequential administrations of inhaled D-mannitol.

Subjects were to be administered 40 mg capsules of inhaled mannitol in a stepwise fashion via the RS01 HR dry powder inhaler device, starting with one capsule, followed by a further two capsules, then a further three and a further four capsules (i.e., a total dose of 400 mg) with spirometry and oxygen saturation measurements being performed between each step to assess bronchoconstriction.

The MTT result was to be judged as follows:

MTT Negative Test (i.e., passed the MTT – subject eligible for randomisation)

1. A total of 400 mg MTT was administered (with no positive criteria being met)
2. FEV₁ fell > 20% (from baseline) at 400 mg but returned to < 20% fall within 15 minutes (without the use of bronchodilators)

MTT Positive Test (i.e., failed the MTT – subject ineligible for randomisation and reported as screen failure in IVRS)

1. O₂ saturation fell below 89%
2. FEV₁ fell > 20% (from baseline) at 40mg, 120 mg or 240 mg
3. FEV₁ fell > 20% (from baseline) at 400 mg and does not return to < 20% within 15 minutes
4. FEV₁ fell > 50% (from baseline) at 400 mg
5. Bronchodilator used at any time during the MTT

MTT Incomplete Test (i.e., subject ineligible for randomisation and reported as screen failure in IVRS)

1. Cough was highly distressing or vomiting occurred during the procedure
2. Any other reason not listed above where test was incomplete

Subjects were required to have a negative MTT result to be randomised.