Do patients with cystic fibrosis participating in clinical trials demonstrate placebo response? A meta-analysis

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DO PATIENTS WITH CYSTIC FIBROSIS PARTICIPATING IN CLINICAL TRIALS DEMONSTRATE PLACEBO RESPONSE? A META-ANALYSIS?

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ABSTRACT

Background. Patients' and families' expectation that a cure for cystic fibrosis (CF) will be found is high. In other debilitating conditions, high expectation has been shown to drive a strong placebo response (PR). Therefore, our goal was to evaluate PR on objective continuous outcomes (FEV_1, BMI) and the CF Questionnaire Revised-Respiratory Domain (CFQR-RD) monitored during randomised clinical trials (RCTs) for CF. **Methods**. We conducted a meta-analysis after a systematic review of the literature carried out to identify RCTs with FEV_1, CFQR-RD and BMI as outcome measures. The standardised mean difference (SMD) was calculated to estimate the PR. A meta-regression analysis was conducted to assess other contributing factors on PR such as study design, trial duration, patient age and disease severity. **Results**. Out of 289 RCTs found in the search, we identified 61 articles (published from 1987 to 2017) with respectively 59, 17 and 9 reporting FEV_1, CFQR-RD and BMI at the start and at the end of the RCTs. No significant PR was found on FEV_1 or CFQR-RD. However, a small but significant PR was found on BMI (SMD, 0.09 (95% CI (0.01; 0.17); p=0.03). **Conclusion**. The PR seems higher when measuring BMI. However, it is not clear whether this improvement can be explained by a PR alone

ABBREVIATIONS

BMI: body mass index

CI: confidence interval

CF: cystic fibrosis

CFTR: cystic fibrosis conductance transmembrane regulator

CFQR-RD: Cystic-Fibrosis Questionnaire Revised-Respiratory Domain

FEV_1: forced expiratory volume in one second

FVC: functional vital capacity

HRQOL: health-related quality of life

PPE: perceived placebo effect

PR: placebo response

RCTs: randomised controlled trials

REML: restricted maximum likelihood estimator

1. Introduction

Because of the progressive and lethal nature of the disease, patients with CF and their families have high expectations that a cure will be found (1). In diverse medical disorders ranging from Alzheimer disease to asthma, high expectation has been shown to drive a strong placebo response (PR) (2).

The true placebo effect is known as "any effects attributable to a pill, potion or procedure but not to its pharmacodynamics or specific properties" (3), with possible benefit and improvement of symptoms. While some evidence illustrates that a true placebo effect is biologically modulated by neurotransmitters (2, 4) associated with specific brain structures (4), its psychological contributors could be explained by both conscious and subconscious mechanisms (5, 6).

Since 1955 with Beecher's statement on the "true" placebo effect, this term has regularly been misinterpreted and confounded with the "perceived placebo effect" or the "placebo response" (7). The PR, the term we will use in this article to avoid any confusion with the placebo effect, equals the "true" placebo effect (8) plus other factors that may explain the improvement or worsening of the patients' outcomes in the placebo arm of clinical trials. This includes (1) the disease's natural history and its possible spontaneous regression (i.e. regression to the mean or intra-subject variability), (2) concomitant treatments, (3) experimental subordination (the subject learns the expected effects and thus tells the expected response) and (4) conditioned responses (5).

In CF, patients and family's expectations may interfere with the PR on several of the above listed factors. However, a systematic evaluation of PR in CF has never been addressed (9, 10). This may be of importance for clinicians to better determine the "true" magnitude of the clinical benefit they may expect for their patients. This may also be important for CF

researchers for methodological purposes (power calculation, study design, outcome measure selection).

The aim of this study was therefore to determine the PR based on three continuous outcomes considered as particularly relevant in CF: respiratory function measured with forced expiratory volume in one second (FEV_1), quality of life with the respiratory domain of the Cystic-Fibrosis Questionnaire Revised (CFQR-RD) and nutritional status with body mass index (BMI).

2. Material and methods

2.1.Literature search

We performed a literature search using PubMed (US National Library of Medicine, Bethesda, MD, USA) and the Cochrane Library (John Wiley and Sons, Chichester, UK) focusing on placebo-controlled RCTs in patients with CF. The last bibliographic search was done on December 12th, 2018. We used the following terms: “placebo AND cystic fibrosis AND randomised controlled trial” as well as “cystic fibrosis AND placebo” and filtered the type of study (“clinical trial” for PubMed and “trial” for the Cochrane Library).

2.2.Selection of meta-analyses

Criteria for inclusion were randomised double-blind placebo-controlled trials in patients with CF of any age and without a lower limit for the date of publication. The age limit between adults and children was set at 18 years old. Eligible interventions were all pharmacological treatments excluding homeopathic treatments, specific diets and vitamin supplementation.

Our research was restricted to studies published in English or French.

2.3.Data extraction

For each study included, the following information was extracted and entered in the database: (1) date of publication, (2) design of the study (randomisation, blinding, parallel group or cross-over), (3) duration of the study, (4) patients' characteristics (adults, children or both; sex, age, number of patients included in placebo and treatment arms), (5) the drug assessed and its therapeutic class, (6) drug doses, (7) change from baseline to the end of the study for three continuous outcomes in the placebo and treatment arms: FEV_1, BMI, health-related quality of life outcomes with the respiratory domain of the CF questionnaire revised (CFQR-RD), (8) percentage of exacerbations during the study for each arm when available, (9) CF lung disease severity based on baseline FEV_1 value when available, (10) CFTR gene mutations if given, (11) any adverse event in both arms if available as well as withdrawals for any adverse event and (12) concomitant treatments.

Data were extracted independently by two authors (JC and VV) and then compared. Inconsistencies were resolved by consensus.

2.4.RCT quality assessment

The quality of the RCTs was estimated with the Cochrane assessment risk of bias (15) and the five-point scoring instrument developed by Jadad and Enkin (11-13).

2.5.Type of pharmacological interventions

We classified pharmacological interventions during RCTs into one of the five drug categories (the first three being the most frequently explored in RCTs in CF): pulmonary (P), nutrition (N), microbiology/anti-infective (M), basic defect (BD) and other (O).

2.6.Outcome measures

We extracted the change from the start (participant characteristics at study entry) to the end of the trial (even if it did not correspond to the time point evaluation of the study's primary

endpoint) for the three continuous outcomes most commonly used in CF RCTs: FEV_1, BMI and CFQR-RD. FEV_1 and BMI were considered as "objective" outcome measures and the CFQR-RD as a continuous "subjective" outcome measure.

2.7.Dealing with missing data

Since we considered continuous outcomes, when the standard deviation (SD) was missing, we estimated it from the standard error (SE) or confidence interval (CI) (14).

2.8.Statistical analysis

The PR was defined as the difference in the outcome measured in the patients of the placebo arm between baseline and the "end-of-study" time points. To anticipate heterogeneity in the continuous data reporting (FEV_1, BMI and CFQR-RD), we calculated the standardised mean difference (SMD) for each outcome instead of the MD. A positive SMD value indicates an improvement under placebo and inversely for a negative SMD value.

Since heterogeneity was expected, a meta-analytic random effects model (inverse variance method) was used, rather than a fixed-effects model (15). The heterogeneity of the SMD across the studies was assessed using the I^2 statistical test (which can be interpreted as the proportion of the observed discrepancy in the estimation of the effect, within a group of trials, which cannot be accounted for by random variation) (16). Publication bias was assessed by a visual funnel plot.

We conducted a univariate restricted maximum likelihood estimator (REML) meta-regression analysis to assess potential contributors to the PR (17). The following explanatory variables were defined beforehand: (1) type of treatment (dummy variables created, pharmacological intervention of interest coded as 1 and others coded as 0); (2) year of publication; (3) disease severity (dummy variables created); (4) age; (5) population (adults versus children); (6) trial duration; (7) design of the study (cross-over design coded 0 and parallel design coded 1). A

QE-test was performed to assess residual heterogeneity when moderators were included. QM was the statistical test for omnibus test coefficients. The coefficients were expressed using the β letter. All analyses were performed with R (R-studio Inc; Version 3.4.4; https://www.r-project.org/).

3. Results

3.1.Description of studies

We identified 1417 reviews. After screening the titles and abstracts, and the exclusion of irrelevant and duplicate studies, 250 reviews were screened (**Figure 1**)**.** Sixty-one RCTs (from 1987 to 2017) were finally analysed **(Table S1** supplemental material). Respectively 59, 17 and 9 RCTs reported results for FEV_1, CFQR-RD and BMI.

There were 58 trials with a parallel design and three with a cross-over design. When the literature search was conducted, there were 29, 14, 12, 3 and 3 RCTs categorised into the pulmonary, microbiology/anti-infective, basic defect, nutrition and "other" categories, respectively. There was a low risk of bias (Cochrane assessment: 1 and Jadad score between 4 and 5) for 29 RCTs (47.5%). It remained undetermined for the others (Cochrane assessment: 2).

Concomitant treatments were specified in 46 RCTs (75.4%). Adverse effects (of any type) were reported in 32 studies (52.5%) with no significant difference between the placebo and treatment arms ($p > 0.05$). Placebo arms contained 4648 patients (2242 males) and the treatment arms included 4917 patients (53.9% males). The mean age in the placebo arm was 19.3 (range, 2.3–32.7) years. The mean trial duration was 207.8 days.

3.2.PR evaluated on FEV_1

PR SMD was estimated at −0.16 in a random effect model (95% CI (−0.24; −0.08); p < 0.000 1) (**Figure 2**), indicating a trend toward deterioration of FEV_1 in the placebo group. A signific ant heterogeneity across studies was identified (I^2 = 81.9%, Q (df = 58) = 319.16, p < 0.0001). The funnel plot was not asymmetrical (**Figure S1-A;** supplemental material).

Univariate meta-regression was then performed to assess the influence of disease or study-related factors on PR assessed on FEV_1 **(Table 1)**. Year of publication did not affect FEV_1 in the placebo group (QM (df = 1) = 2.58, β = 0.01, p = 0.1), nor did age of the participants at inclusion (QM (df = 1) = 0.23, β = −0.003, p = 0.63). The PR on FEV_1 did not differ between adults and children (QM (df =1) = 0.23; p = 0.63), nor did trial duration (QM (df = 1) = 0.02, β = 0 p = 0.88) as well as the type of the intervention (QM (df = 4) = 1.63, p = 0.80) influence PR. Given that the number of studies varied between parallel group (n = 56) and cross-over studies (n = 3), it was not possible to evaluate the influence of study design on PR on FEV_1. Finally, patients' FEV_1 baseline value did not influence PR (QM (df = 2) = 2.68, p = 0.26).

3.3.PR evaluated on CFQ-RD

The overall SMD for CFQR-RD was estimated at −0.11 (95% CI (−0.34; 0.11); p = 0.32) **(Fig ure 3)**. Wide heterogeneity across studies was found (I^2 = 93.6%, p < 0.0001). The funnel plot was not asymmetrical (**Figure S1-B,** supplemental material).

Using univariate meta-regression (Table 1), a greater PR was observed on CFQR in older pati ents (QM (df = 1) = 16.9, β = 0.04, p-value < 0.0001) with one outlier which appeared to driv e the effect. Once removed, the effect of age was no longer significant (QM (df = 1) = 0.97, β = −0.009, p-value = 0.32). PR assessed on CFQR did not differ between adults and children ((QM (df = 1) = 0.89, p = 0.34). Year of publication (QM (df = 1) = 0.007, β = 0.003, p = 0.93), the type of intervention (QM (df = 2) = 1.13, p-value = 0.57), patients' baseline FEV_1 (QM (d f = 2) = 2.76, p-value = 0.25) did not influence PR assessed on CFQR. Trial duration was fou

nd to influence PR assessed on CFQR as well (QM (df = 1) = 79.7, β = −0.002, p-value < 0.00 01). The longer the trial duration, the more the CFQR-RD deteriorated in the placebo group. As observed with age, an outlier drives this effect, since after removal the result was no longe r significant (QM (df = 1) = 0.80, β = 0.0006, p-value = 0.37. Finally, assessing study design on PR using the CFQR-RD was not possible given the low number of trials in each group.

3.4.PR evaluated on BMI

The SMD assessed on BMI was estimated at 0.09 in a random effect model (95% CI (0.01; 0.17); p = 0.03), indicating a trend toward improvement of BMI in the placebo group **(Figure 4).**

The funnel plot was not asymmetrical **(Figure S1-C** supplemental material). Because of the small number of RCTs reporting BMI, we were unable to perform meta-regression to explore the contribution of other factors such as age at inclusion, study design or the type of intervention. Moreover, we were unable to analyse data form children and adults apart, because BMI results were not given separately.

4. DISCUSSION

To our knowledge, this is the first meta-analysis to assess PR in patients with CF investigated in RCTs. The research question behind this work may have implications on the interpretation of the therapeutic effect of past, ongoing and future RCTs for both clinicians and CF researchers.

PR is the combination of the true placebo effect and other factors that may alter the response measured on certain outcomes in patients under the placebo arm of a RCT (18). In a meta-analysis we recently showed that PR was not found to be stronger in children than in adults (19). In the present study, no PR difference was found in patients with CF when assessing

continuous outcomes such as FEV_1 and CFQR-RD. However, a weak but statistically significant PR was found on BMI.

We conducted this meta-analysis on PR by choosing outcomes that were commonly reported and the most relevant regarding CF. CFQR-RD, FEV_1 and BMI are three continuous variables largely used in RCTs and the two latter outcomes in CF clinics. They explore the three most important dimensions of CF disease (i.e. CF-related lung disease with FEV_1; the patient's quality of life with CFQR-RD and nutritional status with BMI) (20-22). Despite the limitations of both FEV_1 and BMI in properly tracking a therapeutic effect in some patients, particularly the youngest patients whose FEV_1 and BMI may be within normal ranges, they remain the outcomes on which clinicians, the FDA and the European Medicine Agency base their decisions to assess the therapeutic effect of an intervention.

We found that there was no evidence of a PR in patients with CF when looking at FEV_1 or CFQR-RD. Both tended to deteriorate between the start and the end of the trials. We found that FEV_1 decreased in the placebo group during RCTs independently of patient- or trial-related factors. With the CFQR-RD the deterioration in the placebo group was influenced by the patient's age and the trial duration mainly because of an outlier trial. These results likely reflect both the progressively deteriorating nature of the CF but also a possible regression to the mean. The genetic origin of the disease and the current standard of care, which mainly treats symptoms, explain that CF remains a slowly progressive medical condition without potential for remission (23). If the deterioration of FEV_1 and CFQR-RD had been mainly driven by the disease progression, a "time-dependent" deterioration would have been found. This was not the case, and the meta-regression analysis showed these two outcomes were not impacted by trial duration. We therefore believe that it reflects the regression to the mean of FEV_1 and CFQR-RD. At the start of the trial, it is likely that patients are selected at their best clinical condition and "regress" to their usual (mean) outcome measures. Regression to the

mean is a well-known factor explaining PR and needs to be considered in order to properly interpret the results observed in placebo arms (18).

However, a small (SMD 0.09; 95% CI 0.01–0.17) but statistically significant PR was detected on BMI. By comparison, but in a very different pathological condition, a PR was observed in young patients with intellectual deficiency with a SMD of 0.468 (SE: 0.150; p = 0.002) (24). Patients with CF are more at risk of stunted growth with low BMI. Our results seem to indicate that patients with CF tended to improve their BMI (i.e. nutritional status) in the placebo group during RCTs. It is not clear whether this improvement can be explained by a PR alone. There are several other reasons explaining that patients improve their BMI during RCTs. Firstly, a 0.09 standardised mean difference on BMI between the two arms of an RCT indicates a very small absolute change in weight between the two groups of patients. Secondly, the improvement of BMI in the placebo group may also reflect (1) the the natural increases of BMI with age (especially among children) (25), (2) regression to the mean (as discussed above) or the impact of other factors known to be part of the PR such as (3) conscious expectancy (the subject learns the expected effects and alters his/her eating behaviour) or (4) conditioned responses or associative learning (26). Retrospectively, it was not possible to distil out true placebo effect from these other factors. Because of the low number of trials included in the meta-regression analysis, we were also unable to explore a number of important contributing factors, particularly age at study entry and the class of the investigational drug tested. Regarding age, several groups have reported that the PR was more pronounced in children suffering neurological or neurodevelopmental conditions (24, 27), probably through a placebo-by-proxy process (28, 29). However, it seems from our group that the magnitude of the PR of children is essentially based on disease, age, study design and the outcome studied (19).

Improving our knowledge on placebo responses in patients with CF may have pragmatic implications for both clinicians and CF trialists: for clinicians, when looking at the results of RCTs and in the perspective of using the tested drug in their patients, to better determine the magnitude of the therapeutic effect they may expect in real life; for CF researchers, this may be of importance for outcome selection, power calculations and study design when using outcomes potentially submitted to placebo responses. Using a "placebo-run-in-period" during RCTs could be useful but it may overestimate the therapeutic benefit (30).

The potential influence of PR on BMI in patients with CF may deserve attention even if BMI is not usually used as a primary endpoint in CF RCTs. For 10 years, the basic defect of CFTR can be partially restored using CFTR potentiators, amplifiers and activators, alone or in combination (31). More than a dozen RCTs using CFTR modulators have been experimented in patients with CF to date. The results of these RCTs have consistently shown an improvement in patients' BMI while sometimes showing a less convincing functional respiratory benefit when looking at FEV_1 changes. The higher "nutritional" benefit can be questioned, and several possible explanations have already been discussed above. Moreover, it is uncertain whether the observed PR for BMI would be consistent across different age groups and how it can be translated in clinic to accurately evaluate clinical benefit.

The main strengths of this study are the originality of the research question and the rigorous method of meta-analysis and meta-regression conducted after an exhaustive literature search. There are a number of limitations, however. Firstly, despite being exhaustive, the number of RCTs available for analysis was relatively low despite the high number of RCTs conducted in patients with CF to date. Indeed, a significant number of RCTs (65 RCTs with missing data at the start and/or at the end of the study and an additional 63 RCTs that reported data as abstracts only) could not be included in the final analysis. Secondly, other respiratory outcome such as pulmonary exacerbation, which is an important patient-related outcome

measure, should be explored because FEV_1 alone does not capture the entire spectrum of CF lung disease. Unfortunately, this analysis was not possible because there were no data available at baseline, making the evaluation of the PR between the start and the end impossible.

In conclusion, this work indicates that patients undergoing RCTs may be submitted to a small but significant PR on BMI. It is not clear whether this improvement can be explained by a PR alone. This study emphasizes the importance of having appropriate control groups in clinical trials.

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Figure 1 – Trial flow chart

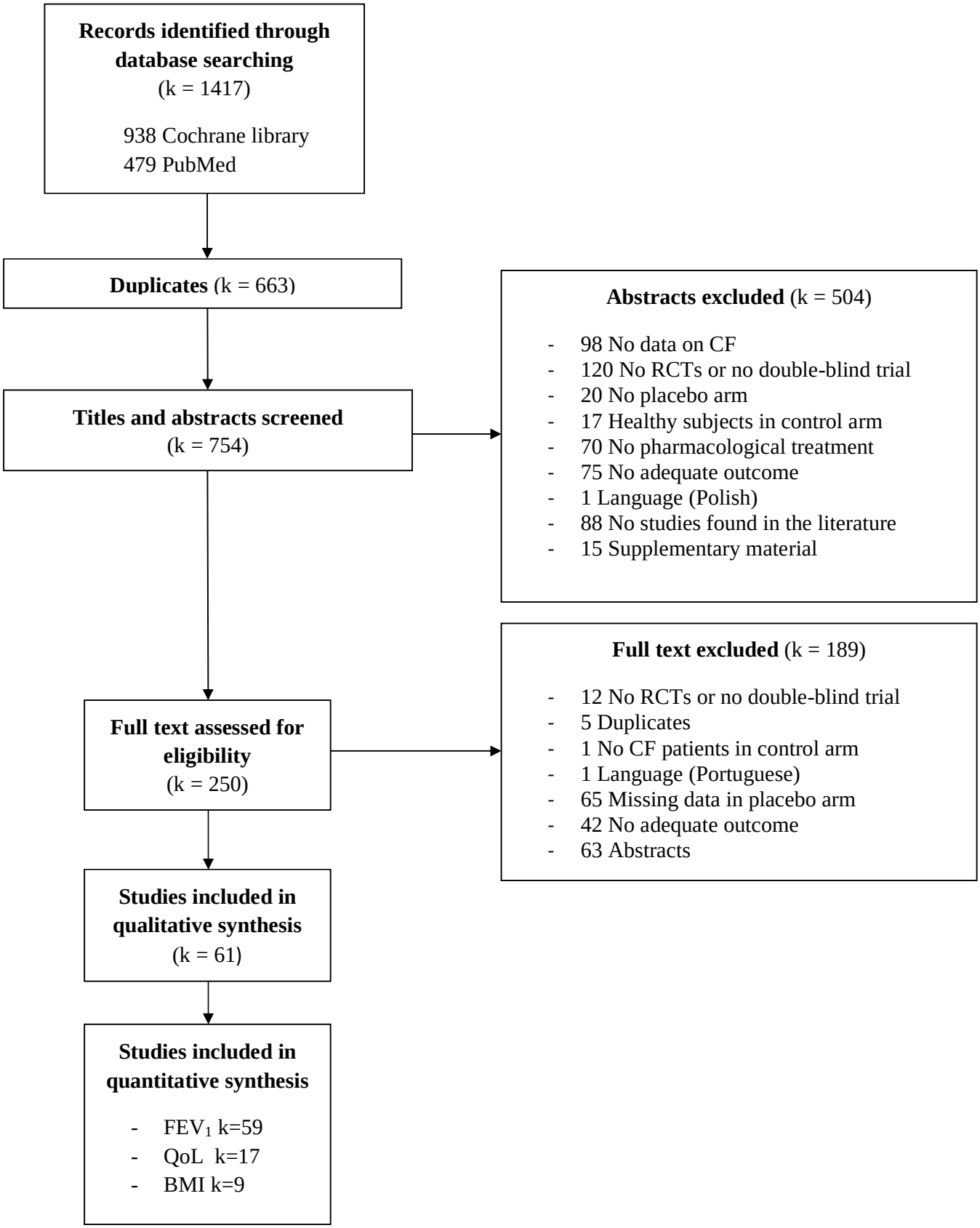
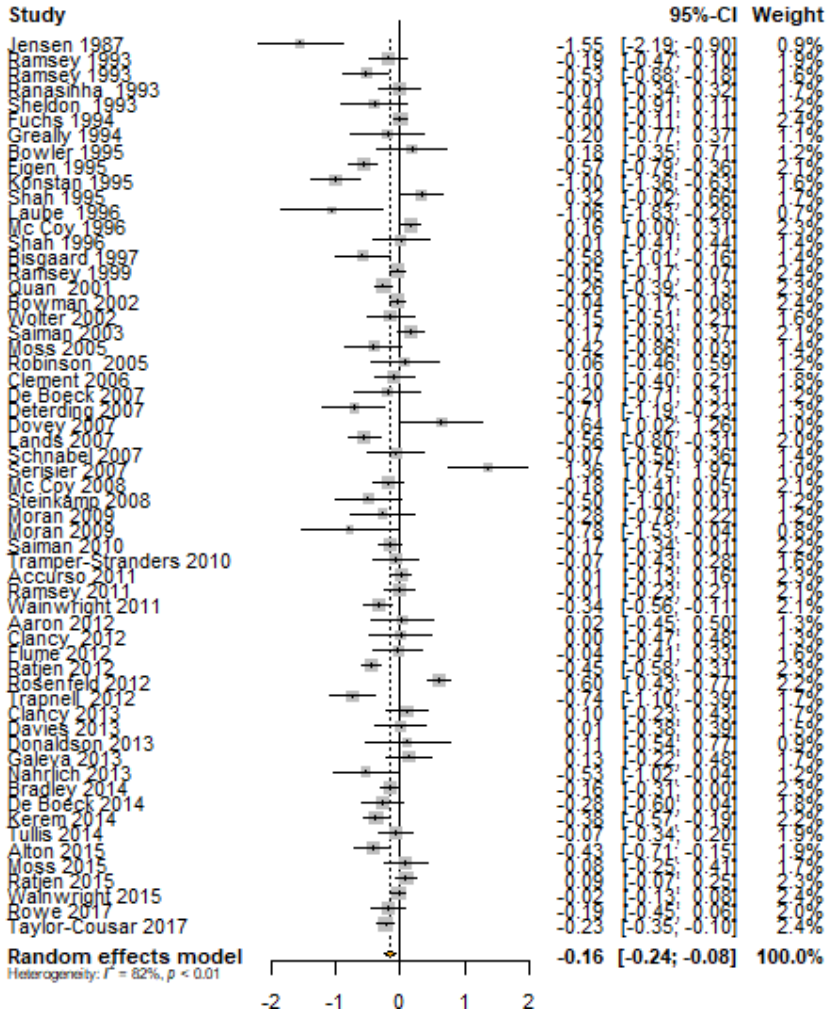
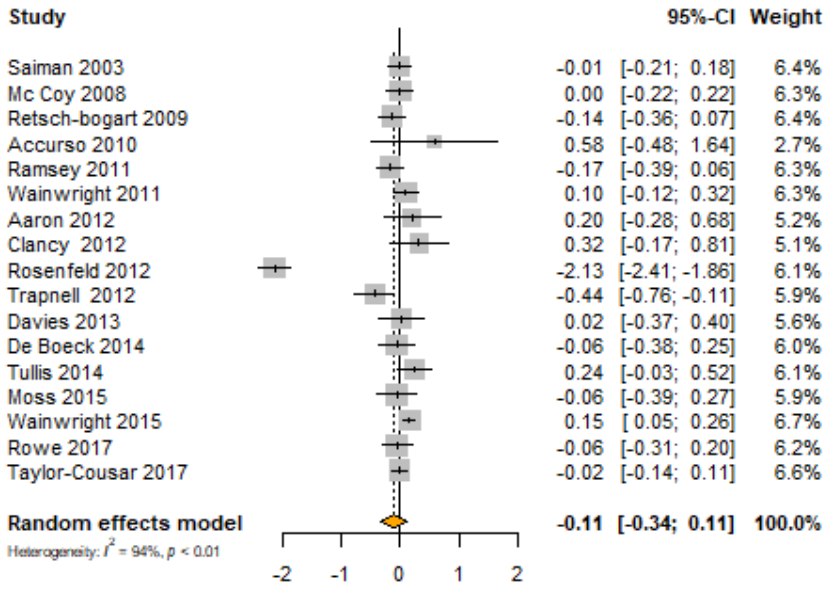


Figure 2 – Forest plot of placebo responses evaluated on FEV_1



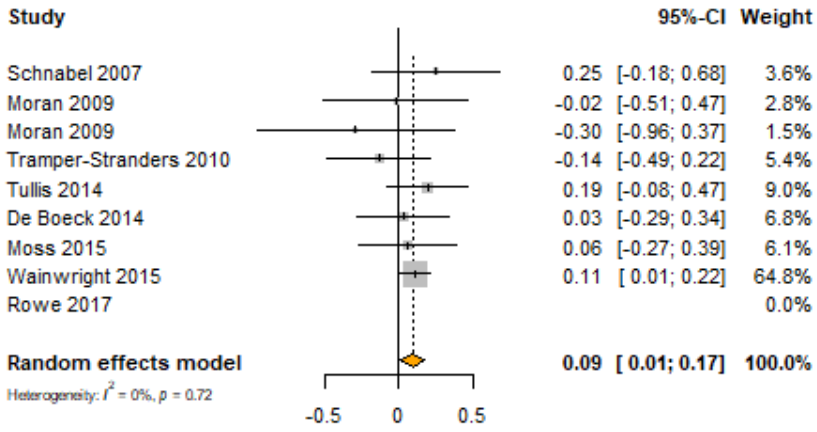
Individual standardised mean differences (SMD) were calculated for each study and are indicated separately on each line. A positive SMD value indicates an improvement under placebo and a negative SMD value a deterioration under placebo. Overall perceived placebo effect SMD was estimated at −0.16 in a random effect model (95% CI, 0.24; −0.08); p=0.0002, indicating a trend toward deterioration of FEV_1 under placebo arm.

Figure 3 – Forest plot of placebo responses evaluated on CFQR-RD



Perceived placebo effect standardised mean difference (SMD) was estimated to −0.11 (95% CI, (−0.34; 0.11); p=0.32). It was statistically non-significant, indicating an absence of PPE on this outcome measure.

Figure 4 – Forest plot of placebo responses evaluated on BMI



Perceived placebo effect standardised mean difference (SMD) was estimated at 0.09 in a random effects model (95% CI, 0.01; 0.17); p=0.03, indicating a small but statistically significant improvement of BMI under placebo arm.

Table 1 Univariate meta-regression of the potential influence of trial- and patient-related factors on perceived placebo effect assessed through FEV_1, CFQR-RD and BMI in RCTs conducted in patients with CF

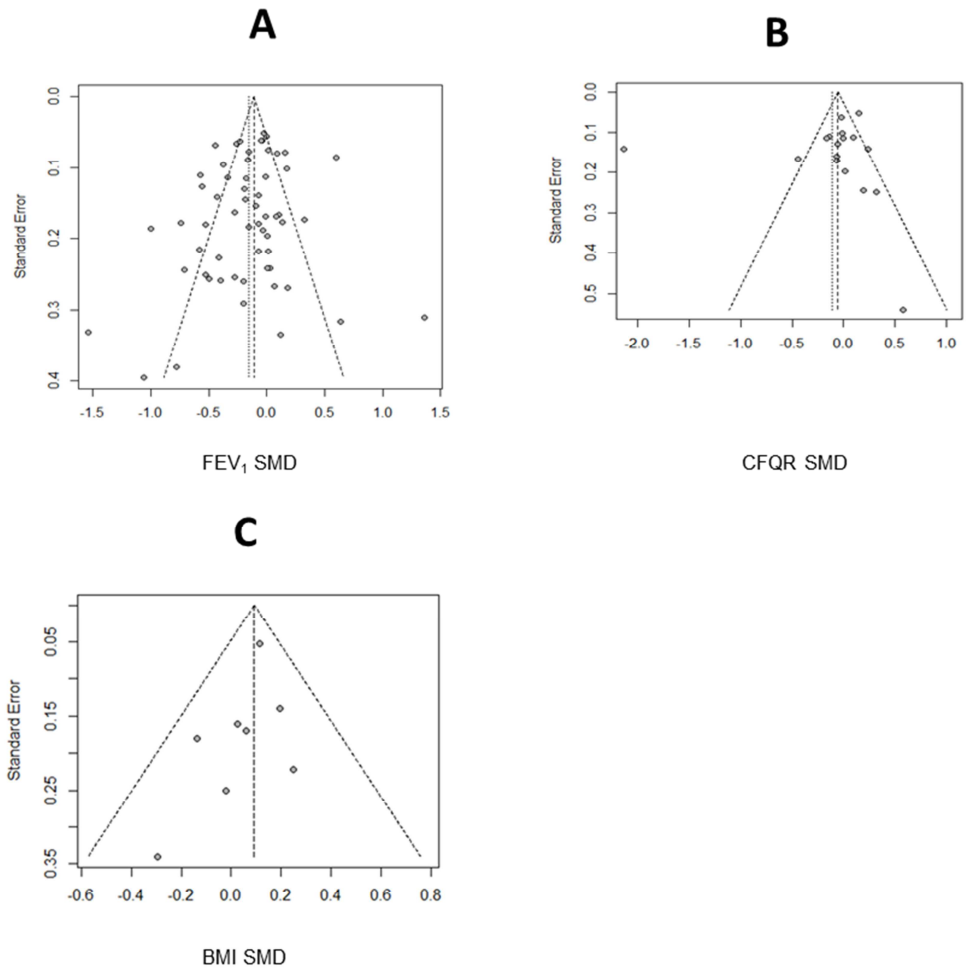
Variables (k = number of studies)	**Categorical data QM (df) (p-value)**	**Continuous data β (p-value)**
FEV_1		
Year of publication (k = 59)	-	0.01 (0.1)
Trial duration (k = 59)	-	0 (0.88)
Age (k = 57)	-	−0.003 (0.63)
CF lung disease severity	2.68 (df=2) (0.26)	-
Classification of drug	1.63 (df=4) (0.8)	-
Trial design	NP	-
CFQR-RD		
Year of publication (k = 17)	-	0.007 (0.93)
Trial duration (k = 17)	-	−0.002(<0.0001)
Age (k = 17)	-	0.04 (0.0001)
CF lung disease severity	2.76 (df=2) (0.25)	-
Classification of drug	1.13 (df=2) (0.57)	-
Trial design	NP	
BMI		
	NP	NP

Univariate meta-regression analysis was used to evaluate the influence of the above factors on PPE through FEV_1 and CFQR-RD: year of publication, trial duration, age, lung disease severity and classification. Trial design could not be integrated into the meta-regression. The meta-regression could not be performed for BMI because the number of available studies was under 10 (k = 9).

Abbreviations: k corresponds to the number of available trials for the outcome of interest. β corresponds to the coefficient of meta-regression for each continuous variable tested. NP: not performed.

Supplementary material

Figure S1



Funnel plot of standardised mean difference (SMD) for FEV_1 (A), CFQR-RD (B) and BMI (C). Funnel plots were not asymmetrical, indicating no publication bias.

Table S1: Studies characteristics

First author	Year of publication	Investigational drug	Drug classification	Patients (n)	Male (n)	Patient age ranges	Study design	Trial duration (days)
Aaron	2012	Itraconazol	Microbiology	17	9	Ch/Ad	Parallel	168
Accurso	2010	Ivacaftor	Basic Defect	4	3	Ch/Ad	Parallel	28
Accurso	2011	Denufosol	Pulmonary	174	85	Ch/Ad	Parallel	168
Alton	2015	pGM169/GL67A	Basic defect	54	29	Ch/Ad	Parallel	365
Bisgaard	1997	Budesonide	Pulmonary	25	NS	Ch/Ad	Parallel	91.25
Bowler	1995	Amiloride	Other	14	5	Ch/Ad	Parallel	15
Bowman	2002	Tobramycin	Microbiology	262	132	Ch/Ad	Parallel	140
Bradley	2014	Tiotropium	Pulmonary	168	96	Ch/Ad	Parallel	84
Clancy	2013	Arikace	Microbiology	36	16	Ch/Ad	Parallel	28
Clancy	2012	Lumacaftor	Basic defect	17	11	Ad	Parallel	28
Clement	2006	Azithromycin	Pulmonary	42	22	Ch	Parallel	365
Davies	2013	Ivacaftor	Basic defect	26	16	Ch	Parallel	168
De Boeck	2007	Fluticasone	Pulmonary	15	9	Ch	Parallel	365
De Boeck	2014	Ivacaftor	Basic defect	39	22	Ch/Ad	Cross-over	56
Deterding	2007	Denufosol	Pulmonary	21	15	Ch/Ad	Parallel	28
Donaldson	2013	Hypertonic saline	Pulmonary	9	5	Ch	Parallel	28
Dovey	2007	Prednisone	Pulmonary	12	9	Ch/Ad	Parallel	28
Eigen	1995	Prednisone	Pulmonary	95	47	Ch	Parallel	1460
Flume	2012	Ivacaftor	Basic defect	28	16	Ch/Ad	Parallel	112
Fuchs	1994	hrDNAse	Pulmonary	325	168	Ch/Ad	Parallel	168
Galeva	2013	Tobramycin	Microbiology	32	13	Ch/Ad	Parallel	29
Greally	1994	Prednisolone	Pulmonary	12	6	Ch	Parallel	84
Jensen	1987	Colistine	Microbiology	20	11	Ch/Ad	Parallel	90

First author	Year of publication	Investigational drug	Drug classification	Patients (n)	Male (n)	Patient age ranges	Study design	Trial duration (days)
Kerem	2014	Ataluren	Basic defect	116	58	Ch/Ad	Parallel	336
Konstan	1995	Ibuprofen	Pulmonary	43	24	Ch/Ad	Parallel	365
Lands	2007	Ibuprofen	Pulmonary	72	NS	Ch	Parallel	365
Laube	1996	hrDNAse	Pulmonary	10	3	Ad	Parallel	6
Mc Coy	2008	Aztreonam	Microbiology	76	45	Ch/Ad	Parallel	28
Mc Coy	1996	hrDNAse	Pulmonary	162	82	Ch/Ad	Parallel	91.25
Moran	2009	Repaglinide	Nutrition	16	8	Ad	Parallel	365
Moran	2009	Repaglinide	Nutrition	9	7	Ad	Parallel	365
Moss	2015	Ivacaftor	Basic defect	35	15	Ch/Ad	Parallel	168
Moss	2005	IFNgamma	Other	21	9	Ch/Ad	Parallel	84
Nahrlich	2013	Amitriptylin	Other	18	8	Ch/Ad	Parallel	28
Quan	2001	hrDNAse	Pulmonary	235	121	Ch	Parallel	672
Ramsey	1999	Tobramycin	Microbiology	262	132	Ch/Ad	Parallel	140
Ramsey	1993	Tobramycin	Microbiology	35	16	Ch/Ad	Cross-over	28
Ramsey	2011	Ivacaftor	Basic defect	78	38	Ch/Ad	Parallel	168
Ramsey	1993	hrDNAse	Pulmonary	48	26	Ch/Ad	Parallel	42
Ranasinha	1993	hrDNAse	Pulmonary	35	20	Ad	Parallel	10
Ratjen	2015	Tiotropium	Pulmonary	155	90	Ch/Ad	Parallel	84
Ratjen	2012	Denufosol	Pulmonary	233	126	Ch/Ad	Parallel	336
Retsch-Bogart	2009	AZLI	Microbiology	84	45	Ch/Ad	Parallel	28
Robinson	2005	hrDNAse	Pulmonary	14	8	Ch	Parallel	91.25
Rosenfeld	2012	Hypertonic saline	Pulmonary	163	92	Ch	Parallel	1460
Rowe	2017	Ivacaftor-Lumacaftor	Basic defect	63	32	Ad	Parallel	56
Saiman	2010	Azithromycin	Pulmonary	129	70	Ch	Parallel	168
Saiman	2003	Azithromycin	Pulmonary	98	52	Ch/Ad	Parallel	168

First author	Year of publication	Investigational drug	Drug classification	Patients (n)	Male (n)	Patient age ranges	Study design	Trial duration (days)
Schnabel	2007	Somatotropin	Nutrition	21	NS	Ch	Parallel	168
Serisier	2007	Albuterol	Pulmonary	20	9	Ad	Cross-over	0.29
Shah	1995	hrDNAse	Pulmonary	35	16	Ch/Ad	Parallel	15
Shah	1996	hrDNAse	Pulmonary	21	NS	Ch/Ad	Parallel	15
Sheldon	1993	Ciprofloxacin	Microbiology	16	10	Ad	Parallel	365
Steinkamp	2008	Azithromycin	Pulmonary	17	7	Ch/Ad	Parallel	56
Taylor-Cousar	2017	Tezacaftor-Ivacaftor	Basic defect	256	131	Ch/Ad	Parallel	168
Tramper-Stranders	2010	Colistin + Ciprofloxacin	Microbiology	31	15	Ch	Parallel	1095
Trapnell	2012	Fosfomycin/Tobramycin	Microbiology	40	27	Ad	Parallel	28
Tullis	2014	Aztreonam	Microbiology	52	35	Ch/Ad	Parallel	168
Wainwright	2011	Aztreonam	Microbiology	81	44	Ch/Ad	Parallel	28
Wainwright	2015	Lumacaftor/ivacaftor	Basic defect	371	187	Ch/Ad	Parallel	168
Wolter	2002	Azithromycin	Pulmonary	30	20	Ad	Parallel	91.25

Descriptive features of the studies included in the placebo-controlled trials of the meta-analysis. Ch: children; Ad: adult; IFN: interferon; hrDNAse: human recombinant DNAse; pGM169/GL67A: name of the liposomal vector