# CLINICAL STUDY REPORT

## A double-blind, randomised, placebo-controlled cross over study of inhaled alginate oligosaccharide (OligoG) administered for 28 days in subjects with Cystic Fibrosis.

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| **Protocol code:** | SMR-2984 |
| **EudraCT no:** | 2014-000844-13 |
| **Investigational Product:** | OligoG CF-5/20 - Guluronic acid rich oligosaccharide derived from alginate polysaccharide (short-form OligoG) |
| **Indication:** | Cystic fibrosis |
| **Development Phase:** | II |
| **Study Initiation Date:** | FPFV: 30 Dec 2014 |
| **Study Completion Date:** | LPLV: 16 Dec 2016 |
| **Report Completion Date:** | Final version 1.0: 12 Sep 2018 |
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**GCP STATEMENT**
This study was conducted in compliance with Good Clinical Practice, according to the ICH Harmonised Tripartite Guideline.

**CONFIDENTIALITY STATEMENT**

# 2 SYNOPSIS

**Title of Study:**

A double-blind, randomised, placebo-controlled cross over study of inhaled alginate oligosaccharide (OligoG) administered for 28 days in subjects with Cystic Fibrosis.

**Co-ordinating Investigator:**

Dr. Tacjana Pressler, Rigshospitalet, Copenhagen, Denmark

**Study Centre(s)*:**

- Site 20801: Dr. Tacjana Pressler, Rigshospitalet, Copenhagen, Denmark
- Site 75201: Dr. Marita Gilljam, Sahlgrenska Universitetssjukhuset, Göteborg, Sweden
- Site 75202: Dr. Lena Hjelte, Karolinska Universitetssjukhuset, Stockholm, Sweden
- Site 27601: Dr. Silke van Koningsbruggen-Rietschel, University Hospital, Cologne, Germany
- Site 27602: Prof. Rainald Fischer, Pneumologische Praxis Pasing, Munich, Germany
- Site 27603: Dr. Susanne Nährig, LMU, Munich, Germany
- Site 27604: Dr. Nico Derichs, Christiane Herzog Zentrum, Charité Berlin, Germany
- Site 27605: Dr. Olaf Eickmeier, University Hospital, Frankfurt a.M., Germany
- Site 27606: Dr. Felix C. Ringshausen, MHH, Hannover, Germany
- Site 27607: Dr. Joachim Riethmüller, University Hospital, Tübingen, Germany
- Site 82601: Dr. Martin Walshaw, Heart and Chest Hospital, Liverpool, UK
- Site 82602: Dr. Mary Carroll, General Hospital, Southampton, UK
- Site 82603: Dr. Jane Davies, Royal Brompton and Harefield NHS Foundation Trust, London, UK
- Site 82604: Dr. Gordon MacGregor, South Glasgow University Hospital, Glasgow, UK
- Site 82605: Prof. Alan Knox, City Hospital, Nottingham, UK
- Site 82606: Dr. Damian Downey, City Hospital, Belfast, UK
- Site 82608: Dr. Charles Haworth, Papworth Hospital, Cambridge, UK
- Site 57801: Dr. Pal Leyell Finstad, University Hospital, Oslo, Norway

*An additional site 82607 (Hull, UK) was planned but never initiated.

**Publication (reference):**
N/A

| **Studied Period (years):** | **Clinical Phase:** |
|---|---|
| Date of first enrolment: 30 Dec 2014<br>Date of last patient last visit: 16 Dec 2016 | Phase 2 |

**Objectives:**

*Primary:*

- To demonstrate efficacy of inhaled OligoG measured by Forced Expiratory Volume in one second (FEV1) and supported by secondary endpoints including Mucociliary and Cough Clearance (MCC), Lung Clearance Index (LCI), Rheology, Microbiology and Quality-of-Life.

*Secondary:*

- To demonstrate the safety and tolerability of inhaled OligoG as a dry powder for inhalation after multiple dose administration.
- To evaluate patient compliance with treatment.

**Methodology:**

*Study design:*

This was a randomised, placebo-controlled cross-over multi centre study to demonstrate efficacy and safety of inhaled alginate oligosaccharide (OligoG) for 28 days in subjects with Cystic Fibrosis. The aim of the study was to demonstrate superiority of OligoG treatment compared to placebo treatment in terms

of FEV1 values. A total of 90 patients were screened at centres in Denmark, Germany, Norway, Sweden and the UK. Of the screened patients 86 were given a test administration of study drug; 4 patients failed the eligibility criteria before administration of the test inhalation. A total of 65 patients were randomised and included in the study. Of the randomised patients, 56 successfully completed two 28 days treatment periods, one with OligoG and one with Placebo (and vice versa), separated by a 4 week washout period. Since this was the first patient exposure to a total daily OligoG dosage of 1050 mg (delivered as 3 x 10 capsules per day), the first 12 patients randomised in the study followed a dose escalation pattern for the first 3 days, starting with a total of 10 capsules on day 0 (i.e. 350 mg), followed by a total of 20 capsules on day 1 (i.e. 700 mg) and the final dosage with a total of 30 capsules on day 2 (i.e. 1050 mg). These first 12 patients were followed up with daily telephone calls up to day 5. No adverse reactions were observed by the DMSB for the first 12 patients in the study and therefore all remaining patients were allowed to proceed with the final dosage. Eleven patients with FEV1 between 60% and 100% at screening also had Lung Clearance Index (LCI) assessments at seven study sites; whilst 14 patients underwent Mucociliary and Cough Clearance (MCC) assessments at three sites**.**

Patients randomised at sites in UK and Germany (DE) that completed the study according to the protocol were eligible to be included in an additional retrospective data collection to allow for assessment of the number of pulmonary exacerbation these patients experienced 6 months pre and 6 months post treatment with OligoG (protocol amendment 2). A total of 40 patients were included in the retrospective data collection.

**Number of Subjects (total and for each dosage):**

A total of 90 patients were screened across 18 sites. A total of 86 patients were given a test administration of study drug with 65 patients randomised 1:1 to treatment sequence, OligoG/placebo (32 patients) or placebo/OligoG (33 patients). Nine patients were withdrawn and 56 patients completed the study, 40 of which were included in the retrospective data analysis.

**Diagnosis and Criteria for Inclusion:**

Inclusion Criteria*:*

In order to participate in the study, the patient must have met all of the following inclusion criteria: The inclusion criteria were verified at the screening visit (Visit 1) and re-confirmed at the start of treatment/baseline visit (Visit 2):

1. Male or female with a confirmed diagnosis of cystic fibrosis defined by:
    a. Clinical features consistent with the diagnosis of CF (Rosenstein BJ and Cutting GR 1998); and sweat chloride ≥60 mmol/L by pilocarpine iontophoresis;
    or
    b. Genotypic confirmation of CFTR mutation
2. Aged 18 years or older
3. Diagnosed Pseudomonas aeruginosa (PA) infection within the subject medical history. For the study as a whole, at least 35 included subjects should be chronically infected with PA according to the following criterion:
    Based on sputum or cough swabs over the last 12 months, subjects must have PA cultured on
    a. ≥ 2 occasions;
    And
    b. ≥ 50% of samples tested.
4. FEV1 must, at Screening (Visit 1), be between 40%-100% of the predicted normal value following adjustment for age, gender and height according to the GLI equation (66). For

subjects to be included in the LCI assessment at selected sites, the FEV1 at Screening should be in the range of 60%-100%.

5. At Screening (Visit 1), no clinical or laboratory findings suggestive of significant pulmonary illness, other than CF, which in the opinion of the investigator would preclude participation in the study. In case lab values exceed 3x the upper limit, the subject will be excluded, as per exclusion criterion 14, below except in case of rise in Gamma-GT values, exceeding this threshold. These Gamma-GT cases will be carefully scrutinized alongside other clinical and laboratory data, and after discussion with the medical monitor and the DSMB clinical experts to exclude significant liver injury, the subject may be enrolled in the study.
6. Female subjects of child bearing potential and male subjects participating in the study who are sexually active must use acceptable contraception. Female subjects documented as being of non-child-bearing potential (e.g. infertile or postmenopausal) are exempt from the contraceptive requirements. For the purpose of this study acceptable contraception is defined as:
    a. oral, injected or implanted hormonal methods of contraception; or
    b. placement of an intrauterine device (IUD) or intrauterine system (IUS); or
    c. barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
7. Provision of written informed consent.

Exclusion Criteria

In order to participate in the study, the patient must not have met any of the following exclusion criteria: The exclusion criteria were verified at the screening visit (Visit 1) and re-confirmed at the start of treatment/baseline visit (Visit 2):

1. Changes in underlying therapy (e.g., chest physiotherapy, bronchodilators, NSAIDs, antibiotic agents, pancreatic enzyme preparations, nutritional supplements and DNase) within the 14 days prior to Day 0 (Visit 2). Subjects must be willing to remain on the same underlying stable therapy regimens for the duration of the study until the final follow-up visit at Day 112.
2. Changes in physiotherapy technique or schedule within 14 days prior to Day 0 (Visit 2).
3. Inhaled acetyl cysteine within 7 days prior to Day 0 (Visit 2) until Day 112 (Visit 8).
4. Concomitant use of inhaled mannitol or inhaled hypertonic saline within 7 days prior to Day 0 (Visit 2) and during the treatment periods. Inhaled mannitol or inhaled hypertonic saline can be re-started during the washout period, but have to be discontinued 7 days before the second treatment period starts.
5. Pulmonary exacerbation within 28 days of Screening (Visit 1).
6. Positive microbiological finding of *Burkholderia* sp. in expectorated sputum or cough swab documented within 12 months prior to Screening (Visit 1).
7. Lactose intolerance/milk allergy, A skin test for milk allergy will be performed for lactose intolerance unknowns at screening. Subjects who have previously received inhaled formulations containing lactose without any allergic or tolerance issues are allowed to proceed without a skin test. For subjects demonstrating a positive skin prick test for milk allergy but have no problems with eating milk and lactose products, the decision will be up to the investigator's discretion.
8. On-going acute illness. Subjects must not have needed an outpatient visit, hospitalization or required any change in therapy for other pulmonary disease between Screening (Visit 1) and Day 0 (Visit 2).
9. History of, or planned organ transplantation.
10. Allergic bronchopulmonary aspergillosis (ABPA) in the last 12 months prior to Screening (Visit 1), defined as having received pharmacological treatment for ABPA.

11. Requirement for continuous (24 hour/day) oxygen supplementation.
12. Diagnosed with the G551D-mutation, and currently on concomitant treatment with Ivacaftor (Kalydeco).
13. Initiation of cycled, inhaled tobramycin (TOBI), Colistin or Aztreonam (Cayston) less than 4 months OR less than 2 cycles of treatment prior to Screening (Visit 1). Cycled TOBI, Colistin and/or Aztreonam users are allowed to participate in this study, but subjects who have recently initiated cycled therapies should have at least 2 cycles in the preceding months before being enrolled in this study. Alternating TOBI and Colistin subjects should be starting an 'off-TOBI' period at Day 0 (Visit 2); alternating Colistin OR TOBI and Aztreonam should start an 'off-TOBI' alternatively an 'off-Colistin' period at Day 0 (Visit 2). Patients on cycled Aztreonam should preferably start concurrently with an 'on-Aztreonam'-cycle. Study treatment periods should in any case be phased in line with the antibiotic treatment.
14. Clinically significant abnormal findings or any value exceed 3x the upper limit of normal on haematology or clinical chemistry will exclude the subject from participating in the study except in case of rise in GGT values, exceeding this threshold. These Gamma-GT cases will be carefully scrutinized alongside other clinical and laboratory data, and after discussion with the medical monitor and the DSMB clinical experts to exclude significant liver injury, the subject may be enrolled in the study.
15. Subjects unable to perform pulmonary function tests according to the ATS/ERS criteria.
16. Pregnant or breast-feeding women. A negative urine pregnancy test must be demonstrated in females of child-bearing potential at Screening (Visit 1).
17. Subjects who have participated in any clinical trial within the 28 days (or shorter than 5 half-lives of the investigational drug) prior to Screening (Visit 1).
18. Subjects with documented or suspected, clinically significant, alcohol or drug abuse as per Investigator's discretion.
19. Current malignant disease (with the exception of basal cell carcinoma and cervical neoplasia).
20. Any serious or active illness incl. psychiatric diseases, which in the opinion of the Investigator, would interfere with subject treatment, assessment, or compliance with the protocol.
21. Subjects not willing/able to follow the study instructions.
22. DPI intolerance, active or placebo.

**For MCC sites only:**

23. Smoking. A negative Cotinine test must be demonstrated at Screening (Visit 1)
24. Subjects who have any non-removable metal objects such as metal plates, screws etc in their head, neck, chest or abdominal area except for Port-a-Cath®s or other implantable ports.

**Test Product, Dose, Mode of Administration, Batch No.:**

OligoG CF-5/20 (OlgioG) was supplied as a dry powder for inhalation (DPI), approximately 48 mg (35 mg OligoG) in hydroxypropylmethyl cellulose (HPMC) capsules delivered via the Miat Monodose Inhaler. Ten capsules were taken by the study subjects three times daily to deliver a total daily dose of 1050 mg. The OligoG product used was from the following batch code: PMBN14053, PMBN14089, PMBN14116.

**Duration of Treatment:**

OligoG and placebo was each inhaled for 28 days.

**Reference Therapy, Dose, Mode of Administration, Batch No.:**

Placebo (Lactose) was supplied as a DPI, approximately 48 mg in HPMC capsules delivered via the Miat Monodose Inhaler, ten capsules three times daily. The placebo product used was from the following batch code: PMBN1401, PMBN14114.

**Criteria for Evaluation:**

Efficacy:

Primary efficacy evaluation was based on changes in FEV1. Exploratory efficacy variables included changes in Mucociliary and Cough Clearance (MCC); Lung Clearance Index (LCI), Microbiological (culture and culture independent) measurements including *Pseudomonas aeruginosa* density in expectorated sputum; Sputum Rheology, other lung function tests and Quality of Life from Baseline to the end of the treatment (and any other visit). Protocol amendment 2 allowed retrospective assessment of pulmonary exacerbation frequencies, hospitalisations and antibiotic treatments in study subjects during the 6 months pre and 6 months post study participation.

Safety:

The safety and tolerability data collected in this study included Adverse Events, rate of premature withdrawal from the study, clinical laboratory parameters (biochemistry and haematology), vital signs, ECG, physical examinations, pulmonary exacerbation rates, use of rescue bronchodilators and concentration of OligoG in sputum and plasma.

**Statistical Methods:**

The methods for statistical analysis were described in the Clinical Trial Analysis Plan (CTAP), Version 1.0, dated 21st October 2016, and in the CTAP for Protocol amendment 2, version 2.1, dated 18th October 2017.

**SUMMARY – CONCLUSIONS**

A total of 90 patients were screened for the study. Of these, 86 patients received a test administration of the study drug at V1, and 65 patients were randomised to receive treatment.

Thirty two patients were randomized to receive OligoG in the first treatment period and placebo in the second treatment period, whilst 33 patients were randomized to receive placebo in the first treatment period and OligoG in the second treatment period. Each treatment period was 28 days followed by 28 days wash-out. The results indicated there was a sustained effect that lasted throughout the washout period for several subgroups, consequently data from day 56 are also reported for several of the parameters.

**Efficacy Results:**

**Lung function**

Primary efficacy evaluation was based on changes in forced expiratory volume in one second (FEV1). Statistically significant improvement in the forced expiratory volume in one second (FEV1) was not reached in the ITT population. However, trends were shown in subgroup analyses of OligoG in comparison to placebo for tobramycin, continuous inhaled antibiotics, <100% adherence, and younger patients (<25 yrs old).

- OligoG treatment with tobramycin showed improved lung function (FEV1) of 9.7% at day 28 (p=0.0010) and 15.8% at day 56 (p=0.0095).
- Patients on continuous inhaled antibiotics and <100% adherence to OligoG also showed an 8.6% improvement in FEV1 at day 28 (p=0.0190), and 12.8% at day 56 (p=0.0204).
- There was also a clear tendency for FEV1 improvement after OligoG treatment in those patients who took less than the full dose of the drug (< 100% adherence), with 5.5% improvement in FEV1 at day 28 (p=0.0738), and 8.5% improvement in FEV1 at day 56 (p=0.0690).

- OligoG treatment in younger patients did not show significant effects although a 4.3% increase in FEV1 was noted at 28 days, which increased to 9.5% at 56 days.

In the ITT population there was a pronounced drop in FEV1 at day 14, followed by recovery to baseline by day 28. Interestingly, this was not observed in those patients who were subsequently identified to have taken less than the full dose of OligoG (< 100% adherence). These findings support the known mechanism of action of OligoG in reducing elevated mucus viscosity and potentiating the activity of antibiotic therapies, since the drop in FEV1 and other spirometry measures at week 2 was only a transitory reduction in lung function. This is thought to be related to the rapid increase in the mobility of mucus due to the calcium binding effect of OligoG triggering the release and swelling of stagnant mucus plugs. This would initially reduce pulmonary function before the mucus could be expectorated by the patients. These combined subgroup analyses clearly indicate the potential value for OligoG to improve lung function and suggest that a lower OligoG dose may be more beneficial and potentially help to alleviate the initial drop in FEV1.

**Rheology**

Rheology measurements of viscosity, elasticity and phase angle in expectorated sputum, did not show a statistically significant improvement in the ITT population. However, there was a statistically significant improvement observed at 0.1 Hz (p= 0.0311) in the modified ITT population at 2 weeks of treatment. A similar finding was observed at 0.1 Hz for the modified ITT on tobramycin (p=0.0455), which may reflect the combined effects of OligoG on rheology, biofilm disruption, and antibiotic potentiation. This clear effect of OligoG treatment was even more pronounced in patients <25 yrs old which showed a marked improvement in phase angle at 0.1 Hz (p=0.0014) at the end of treatment (28 days), indicating that the sputum viscosity is reduced and more liquid after treatment with OligoG. This supports what has previously been reported for the mechanism of action of OligoG (Ermund et al 2017).

**Mucociliary and Cough Clearance (MCC)**

OligoG did not demonstrate a significant improvement in mucus clearance, as assessed by gamma scintigraphy, despite improved lung function in certain patient subgroups and improved sputum rheology. However, from analysis of the central lung to peripheral lung ratio (C/P ratio) of isotope deposition at each study visit, there was a trend towards more peripheral deposition following OligoG treatment when compared to baseline. This more peripheral deposition suggests that the smaller airways were more open after OligoG treatment. That this effect was not reflected in more effective clearance could be due to the MCC assay being best suited to capture effects on larger airway cilia driven clearance. An analysis of peripheral lung clearance, which is less confounded by deposition changes, showed a trend toward faster peripheral lung clearance with OligoG.

**Pulmonary Exacerbation rate**.

There was no apparent difference in exacerbation rates between OligoG and placebo during the clinical trial. However, in a retrospective study where exacerbations were recorded for the 6 months either side of the trial period, a trend towards fewer exacerbations in the post study period was observed with 34 PE's reported in the pre-treatment period versus 24 PE's in the post treatment period. This represents a mean reduction of 0.25 PEs/patient, or a 29% reduction in PE's (p = 0.0629). This is an interesting observation, although it is not clear whether this reduction was the direct result of OligoG treatment alone.

**Microbiology**

Although the numbers from culture microbiology analysis were small there was a reduction (> 1 log) in mean CFU counts for *P. aeruginosa* in some patients after OligoG treatment. However, a more significant reduction in microbial burden was expected given the significant body of literature highlighting the antimicrobial properties of OligoG (Kahn et al 2012; Powell et al 2013; 2014; 2018; Pricthard et al 2017; Jacks et al 2018). Subsequent investigation identified independent evidence that lactose inhibits *Pseudomonas aeruginosa* and other CF respiratory pathogens adhesion to lung epithelial cells and potentiates the activity of antibiotics (Bucior et al 2013; Chemani et al 2009; Wright et al 2010; 2012). Additional studies have also identified a role for metabolites, such as lactose enhancing antibiotic susceptibility to antibiotics such as tobramycin (Allison et al 2011; Meylan et al 2017). In order to minimize the risk of unblinding in the current cross-over trial, the lactose placebo was administered in the same dose (1050mg per day) as the dry powder formulation of the active drug. Retrospective analysis suggests that this high dose of lactose may not have been the best choice of placebo to evaluate microbiological effects of OligoG in this particular study.

**Safety Results:**

There were no safety issues identified in this study and confirms early studies that the active drug is safe to use in this study population.

**Conclusion:**

The results from this clinical study demonstrated that repeated inhalation of OligoG DPI was safe in CF patients. Although the study did not meet its primary objective, the results are supportive of OligoG efficacy in mobilizing mucus, improving lung function (FEV1), and potentiating antibiotics, which supports the benefit of OligoG treatment in CF. The findings also indicate that a reduction in the high dose of OligoG administered in the current study may be beneficial. A planned study with lower doses of OligoG over a longer period (eg., 3-6 months), in patients currently taking inhaled antibiotics has been designed to test these assumptions.