Name of sponsor/company: Mukoviszidose Institute gGmbH In den Dauen 6 53117 Bonn / Germany Phone: +49 / (0)228 / 98780-0 Fax: +49 / (0)228 / 98780-77 E-mail: impactt@muko.info	Individual study table referring to part of the dossier Volume: N/A Page: N/A	(For National Authority Use only)
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Name of active ingredient: avian polyclonal IgY antibody against Pseudomonas aeruginosa (Anti-Pseudomonas IgY)		

Title of study:
Prospective randomized, placebo-controlled, double blind, multicenter study (phase III) to evaluate clinical efficacy and safety of avian polyclonal anti-Pseudomonas antibodies (IgY) in prevention of recurrence of Pseudomonas aeruginosa infection in cystic fibrosis patients

Versions of study protocol:
Version 1.5, 17 OCT 2013; approval on 13JAN2014 by Paul Ehrlich Institut
Version 1.4, 18 MAR 2012; approval on 20 APR 2012 by Paul Ehrlich Institut
Version 1.3, 30 SEP 2011; approval on 04 NOV 2011 by Paul Ehrlich Institut
Version 1.1, 25 JUL 2011; first approval on 25 AUG 2011 by Paul Ehrlich Institut
Version 1.0, 18 MAR 2011; was amended without prior approval during initial submission
Note: Protocol version 1.2 is not filed in any official study file. Version 1.2 was used as draft version number when protocol 1.1 was amended. After a final version had been agreed on, this final version was given new version umber 1.3. Protocol version 1.2 was never submitted to any Ethics committee or Competent authority.

Registration numbers:
PEI (Vorlagenummer): 1319/01
EudraCT: 2011-000801-39
ISRCTN:

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Publication (reference):
Publication in preparation.

Studies period (years): 2011-2017 (date of first enrolment) first patient screened: 14NOV2011 first patient included: 29NOV2011 (date of last completed) last patient, last visit: 27JUN2017	**Phase of development**: Phase III

Objectives:
- Primary:
  - The primary objective of the study was to find out, if continuous long-term local application of specific egg yolk antibodies (IgY) directed against PA - initiated after successfully treated acute PA infection can prolong the time to recurrence of a sputum culture positive for PA.
- Secondary:
  - Change in FEV 1.0 from day 0 to each visit
  - Change in BMI from day 0 to each visit
  - Reduction of the number of exacerbations
  - Reduction of the number of days of illness in hospital and at home, i.e. out of school or work
  - Control of use of antibiotics, especially anti-pseudomonas antibiotics –measured as days with antibiotic treatment
  - Change in values of serologic tests for PA precipitins screening to each visit (if applicable)

Methodology:
This trial was a prospective randomized, placebo-controlled, double blind, multicenter and multinational phase 3 study to evaluate clinical efficacy and safety of avian polyclonal anti-Pseudomonas antibodies (IgY) in prevention of recurrence of Pseudomonas aeruginosa (PA) infection in cystic fibrosis patients by means of passive mucosal immunization.
The trial was conducted at 47 sites in Germany, Belgium, Ireland, Sweden, Hungary, Poland, Austria, Italy and Spain. Patients from 5 years of age were included if they had a proven diagnosis of cystic fibrosis and had had a prior bronchopulmonary infection with Pseudomonas aeruginosa in the past 2 years that had been eradicated at the time of inclusion into the study (for detailed inclusion criteria please see below). Patient recruitment took place from November 2011 to June 2015. The study duration in the individual patient was until the next infection with P.aeruginosa was diagnosed, or two years (in case of no infection).

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All patients/parents or their legal representatives provided written informed consent. The trial as well as the trial documents were approved by the responsible competent authorities in every participating country and by the independent Ethics committees for each trial site. Safety was monitored by a Data and Safety Monitoring Board. Before starting the screening procedure, the trial was submitted to the trial registry Clinicaltrials.gov (NCT01455675).
The trial had a parallel group design to compare avian Anti-pseud IgY solution with a placebo control solution without non-specific IgY (non-pseud IgY). The specific drug was prepared by extracting IgY from eggs of hens which had been immunized with Pseudomonas aeruginosa. The control was manufactured in the same way, except immunization of the hens beforehand. No activity against PA was detected in the placebo. The study drug was to be gargled and swallowed once a day in the evening. Compliance was checked by monthly phone calls by the study coordinators and by counting the (empty) drug bottles and boxes for drug accountability.
Patients were allocated to one of the two treatments, in a 1:1 ratio , by central fax block-randomization. The randomization list was generated by the KKSD using a validated system, which involved a pseudo-random number generator to ensure that the resulting treatment sequence was both reproducible and non-predictable. From the total of 171 patients that had been randomized, 83 patients were analysed in the treatment group, and 81 patients in the placebo group.
Primary Endpoint of the study was Time from start of treatment (=Day 0) to the first recurrence of PA (Pseudomonas aeruginosa) in the sputum or throat cough swab or endolaryngeal suction. For a listing of all secondary endpoints analyzed in the study, please refer to the „objectives"-section above.
Sputum samples (alternatively throat cough swabs or endolaryngeal suction samples) were taken at every study visit for the primary endpoint analysis. The local microbiology laboratories did a routine assessment of these samples for detection of P.aeruginosa. At certain time points (screening visit, week 52, week 104, and termination visit), samples were also analyzed by a central microbiology lab at RH Copenhagen. In addition, all samples found to be PA-positive by local labs, had to be confirmed by the central lab as well.

Number of patients (planned and analyzed):

Inclusion of 180 patients was planned, in order to analyze 144 patients with 91 events.

A total 171 patients were randomized, and 164 patients were eligible for analysis of the primary endpoint (81 patients of the placebo group, and 83 patients of the treatment group) ; 7 patients did not receive the allocated intervention (6 patients declined to participate, and 1 patient was diagnosed to already have a PA infection at the start of the study). In these 164 patients, 64 events (i.e., PA detection) were observed.

Diagnosis and main criteria for inclusion:

- CF patients diagnosed according to specific clinical features, and either a positive sweat chloride in double proofs or presence of disease-associated CFTR mutations in both alleles
- Males and females ≥ 5 years of age (being able to gargle)
- CF patients with a FEV1 value between 50% and 130% of predicted (according to Knudson formula)
- CF patients who have had one to several sputum or throat cough swabs or endolaryngeal suction cultures positive for PA within the last three years and in whom *PA* had been successfully eradicated.
- Sputum / throat cough swab/ endolaryngeal suction culture negative for PA on study entry.
- Patients and/ or their legal representatives willing and able to give informed consent/ assent to participate in the study after thorough information.
- Subjects of child-bearing potential who are sexually active must meet the contraception requirements (i.e. oral or injectable contraceptives, intrauterine devices, double-barrier method, contraceptive patch, male partner sterilization, or condoms).

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Test product, dose and mode of administration, batch number:

Both the investigational drug and the reference placebo preparation are solutions (70 ml), which were gargled for 2 minutes every night after tooth brushing and thereafter swallowed. The test product contains 50 mg IgY with an activity against PA of >5 FKU/ml.

Duration of treatment:
Up to 24 months or until next PA infection, whichever was first

Reference therapy, dose and mode of administration, batch number:

The placebo was prepared by an identical manufacturing process as Anti-Pseudomonas IgY, except that the starting material was eggs from hensthat had not been immunized with Pseudomonas aeruginosa.

Criteria for evaluation:

Efficacy:
- Primary:
  - Time from start of treatment (=Day 0) to the first recurrence of PA (Pseudomonas aeruginosa) in the sputum or throat cough swab or endolaryngeal suction.

- Secondary:
  - Change in FEV 1.0 from day 0 to each visit
  - Change in BMI from day 0 to each visit
  - Number of exacerbations
  - Number of days of illness in hospital and at home, i.e. out of school or work
  - Control of use of antibiotics, especially anti-pseudomonas antibiotics –measured as days with antibiotic treatment
  - Change in values of serologic tests for PA precipitins screening to each visit (if applicable)

Safety:
- Good tolerability and comparable number and quality of adverse events like placebo group
- Sputum or throat cough swab or endolaryngeal suction cultures for bacteria and fungi

Definition of study populations

• The **Full Analysis Set (FAS)** consists of all enrolled patients who received at least one dose of assigned treatment. Following the intent-to-treat principle, patients are analyzed according to the treatment assigned by randomization.
• The **Per-Protocol population (PP)** consists of all patients from the Full Analysis Set population without any major protocol deviations who are evaluable for efficacy and have completed a minimum exposure requirement. However, if a patient deteriorated, discontinued for adverse event or died before the minimum exposure requirement could be met, or before he/she could become evaluable for efficacy, that patient will still be included in the Per Protocol Set. The minimum exposure requirement is defined in general as having relative dose

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intensity over the first 2 cycles of treatment of at least 90%. The dose intensity requirement applies to all compounds in the study treatment

• The **Safety population (SAF)** consists of all patients who received at least one dose of study treatment. Patients are analyzed according to the treatment received.

Statistical methods:

Primary Endpoint:

The confirmatory analysis of the primary endpoint was performed for the FAS. Additional efficacy analyses were conducted for the PP-population.

The primary study endpoint was defined as the differences between gargling with Anti-pseudomonas IgY and gargling with placebo with respect to time from day 0 to recurrence of PA in sputum within the period of up to 104 weeks.

The primary efficacy endpoint was analyzed using a log rank test. Superiority of IgY would be claimed if the p-value from the comparison is <0.0115 at the interim, or <0.0464 at the final analysis. The median time to event for each treatment group was derived from a Kaplan-Meier analysis including a 95 % confidence interval for the medians.

Patients without an event were censored at the time of withdrawal, or after 24 months. In addition to the log-rank test an analysis using a Cox proportional hazard model was used in order to estimate the hazard ratio. An explorative analysis of the influence of the history of a PA-infection before study entry (<= 1 year, 1-3 years before study entry), age and gender, was performed using a Cox proportional hazard model.

Secondary Endpoints:

Analyses for the secondary endpoints were performed for the FAS and for the PP-population. All secondary endpoints were evaluated by using descriptive statistics depending on the type of the data. Secondary efficacy endpoints were summarized and presented at each visit separated by treatment group.

Secondary outcomes FEV1 and BMI:

The statistical analysis of these secondary outcomes was performed with mixed effect models. In these models, treatment group, age (adults or pediatrics), gender and time were fixed effects, while the effect of patients was considered as random effects.

Treatment effects were assessed by the interaction between time and treatment. Differences in the slopes between treatment groups will give an indication of treatment effect.

Estimation of model parameters was calculated with REML (restricted maximum likelihood) method. Treatment effect was tested with a likelihood ratio test (LRT) at 5% significant level. 95% confidence intervals were reported for all parameters in the model.

Model checking was performed by residual analysis and strong deviations from the model assumptions were observed. For this reason, a Bayesian mixed effect model, which is robust against residual deviations, was applied for these end points. Posterior distributions for model parameters were calculated by using MCMC (Markov Chain Monte Carlo) computations. The effects of treatment, gender and age were presented by the 95% posterior intervals.

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Secondary outcomes: days in hospitals, days out of school/work and days of use of antibiotics

The statistical analysis of these secondary outcomes was planned to be performed with a Poisson mixed effect model. In this model, treatment group, age (adults or pediatrics) and gender were considered as fixed effects, while centers were considered as random effects. Time in the study was used as an offset to account for the extent of exposure. This model reflects the possibility that we may have extra variability coming from data collected at different centers.

Given that we did not have enough patients within centers, it was not possible to fit the planned Poisson mixed effect model. A Poisson regression model without random effects was fitted, but did not fit the data well and it was rejected.

In order to account for the over-dispersion coming from the multi-center data collection a Negative Binomial regression model was used. Model fitness was measured by the residual deviance and residual analysis. The model choice was based on AIC (Akaike Information Criteria).

Secondary outcome: number of exacerbations

For the number of exacerbations we performed two statistical analyses: 1) by using a dichotomic outcome on the number of exacerbations (yes, no) and 2) by using the original count variable.
The statistical analysis of this secondary outcome was planned to be performed with a Logistic regression mixed effects model for the dichotomic values and with a Poisson mixed effect model. Time in the study was used as an offset to account for the extent of exposure.

In those models, treatment group, age (adults or pediatrics) and gender were considered as fixed effects, while centers were considered as random effects. These models reflect the possibility that we may have extra variability coming from data collected at different centers.

Given that we were not able to recruit enough patients within centers, it was not possible to fit the planned mixed effect models. Therefore, we fitted an overdispersed logistic regression and Negative Binomial regression model to adjust for a possible overdispersion coming from the fact that this is a multi-center trial. Model fitness was measured by the residual deviance and residual analysis. The model choice was based on AIC (Akaike Information Criteria).

Safety analyses

The safety analysis set will be used to address all issues of safety which usually include:
Occurrence of adverse events

- Change in clinical laboratory parameters, including new bacteria or fungi in cultures
- Rate of premature withdrawals
- Other parameters (e.g., baseline characteristics, physical examination, diary results)

Adverse events data were processed in the statistical analysis after coding according to the current version of the MedDRA dictionary which is available at the time coding is started.
Adverse events were presented in summary tables listing these events in code form according to the preferred term. These tables show the number of patients presenting an adverse event and the incidence of its occurrence. Adverse events were grouped by system organ class and stratified by severity and by relation to study treatment.

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Laboratory data
Laboratory data (FEV1, BMI, anti-pseudomonas precipitins, CRP) were presented in tabulated statistical summaries of the raw data.

Summary – Conclusions:

Efficacy results:

Patients' characteristics were equally distributed in both arms.

Primary Endpoint:
The statistical analysis of the primary endpoint shows that we cannot reject the null hypothesis of no difference between the treatment groups (p-value: 0.95). The statistical analysis of the primary endpoint in the PP-population shows similar results (p-value: 0.23).

The samples size calculation was based on the assumption that the expected number of events was 91 in 144 patients. The number of observed events was 64 in 164 patients, which shows that the patient population in the study did not develop PA reinfections as expected.

The observed median time to event in the treatment group was 26.3 months (105.14 weeks/4) in the FAS, and 26.3 months (105.14 weeks/ 4) in the PP-population. The expected median time was 22.5 months. This shows that the study plan was in line with the results of the treatment group. However, the observed median time to event in the placebo group was not reached in both populations during the study (expected median time was 12.5 months). This shows that the placebo group reacted with far less events than expected.

Cox-Regression:
For the FAS, in the model which includes all covariates, the variable FEV1 (less or greater than the median) resulted statistically significant. The covariates included in the best model according to AIC (Akaike Information Criteria) were not statistically significant. In the PP-population, neither the model which includes all covariates nor the best model according to AIC shows that those covariates were statistically significant. The Cox regression analysis is limited by the small number of observed events.

Secondary endpoints:

FEV1
For the fixed effects results for FEV1 in the Bayesian analysis, we found that neither the difference between the intervention groups' intercepts (baseline means), nor the difference in the slopes between treatment groups, which represents the treatment effect, was statistically relevant.
For the random effects results, it was shown, that the random intercept explains 95.682 and the rest of the variability is explained by error measurement and random slope. These results show a large heterogeneity between patients. The results of the PP-population were very similar with the difference that the gender effect was not statistically relevant.

BMI:
For the fixed effects of the BMI in the Bayesian analysis, we found a trend on the mean difference between the intervention groups' intercepts (baseline means), where the treatment group has a larger mean intercept than the control group. However, the 95% posterior interval covers the zero, which means no statistical difference between the groups. There is also a trend to positive treatment effect in the slopes, but the 95% posterior interval

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Name of finished product: N/A		
Name of active ingredient: avian polyclonal IgY antibody against Pseudomonas aeruginosa (Anti-Pseudomonas IgY)		

covers the zero value of no difference. We found that the gender has no effect but age has a strong influence at baseline where adult patients have a larger BMI than children. From the total random variability, the random intercept explains 97.08% and the rest of the variability is explained by error measurement and random slope. These results show a large heterogeneity between patients. The results of the PPP are very similar to the FAS; with the exception of a statistically relevant difference between the means of intervention groups at baseline (the 95% posterior interval excludes the zero value).

Days in Hospital, days out of school/work and days of use of antibiotics

For the analysis of the days in hospital in the FAS, the Negative Binomial model showed neither significant results between the treatment groups nor age and gender groups. For the Days in hospital in the PP-population, only the data of children was used for the analysis. Here the analysis shows that neither the intervention nor the gender are statistical significant.

For the analysis of the days out of school/work, the Negative Binomial model showed no significant results for treatment, but statistically significant influence of age and gender groups. For age and gender groups we found that female and adults tend to have fewer days out of school/work. The results of this analysis are similar to the FAS, with the exception that only age has a statistically significant effect, where adults tend to be less absent to work.

For the analysis of the days of use of antibiotics, the Negative Binomial model showed no significant results for treatment and for age and gender groups. The results of the statistical analysis were similar to those of the FAS.

Number of exacerbations:

For the dicotomic outcome, the over-disperse Logistic regression model showed no statistically significant difference between the intervention groups. Also, the influence of the covariates age and gender was not statistically significant.

The Negative Binomial model showed no significant results for treatment and the other covariates included in the model. The results of the PP population were similar to those of the FAS.

Safety results:
A total number of 1972 adverse events (AEs) was documented, 987 of which were in the placebo group and 980 in the treatment group. The most commonly observed adverse events were abdominal pain, vomiting, pyrexia, nasopharyngitis and upper respiratory tract infection, headache, cough and positive tests for bacteria/fungi other than PA in respiratory cultures. No deaths occurred. Most of all AEs were of mild (77,43%) or moderate (20,95%) severity. The incidence of AEs was similar in the two groups: 77,71% (placebo) vs. 77,14%, and 20,16% (placebo) vs. 20,95%, respectively. There were only few AEs judged to be related to the study drug: 5 adverse events in the treatment group and 20 in the placebo group (based on blinded clinical decision). None of the adverse events judged to be related to the study drug was serious. In two cases, AEs led to premature withdrawal of the patients, one in the placebo and one in the treatment group. Generally, the study drug was well tolerated.

Conclusion:
While the study drug was safe in the investigated patient population, efficacy of Anti-Pseud-IgY could not be shown with the used trial design. This is due to the fact that the placebo group reacted with far less events than expected, whereas results of the treatment group were in line with the study's plan. One potential explanation for this finding could be that the non-pseud-IgY used as comparator is also effective in postponing PA infection

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in a non-specific way. Another possibility is that current treatment has led to an improved time to reinfection in CF patients so that the assumptions made at the point of study planning were not in keeping with the times. These hypotheses shall be investigated in further projects.

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14. December 2018

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14 December 2018