EU Clinical Trials Register

Clinical trial results:
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

Summary

EudraCT number	2011-000801-39
Trial protocol	DE SE BE IT IE HU AT ES
Global end of trial date	27 June 2017

Results information

Result version number	v1 (current)
This version publication date	12 April 2019
First version publication date	12 April 2019
Summary attachment (see zip file)	2018_12_14_IMPACTT_PsAer-IgY_FinalReportSynopsis_V01-F (2018_12_14_IMPACTT_FinalStudyReport_V01-F.pdf)

Trial information

Trial identification

Sponsor protocol code	PsAer-IgY

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01455675
WHO universal trial number (UTN)	-
Other trial identifiers	clinicaltrials.gov: NCT01455675

Notes:

Sponsors

Sponsor organisation name	Mukoviszidose Institute gGmbH
Sponsor organisation address	In den Dauen 6, Bonn, Germany, 53117
Public contact	Sponsor´s Project Manager , Mukoviszidose Institute gGmbH , +49 228987800, impactt@muko.info
Scientific contact	Sponsor´s Project Manager , Mukoviszidose Institute gGmbH , +49 228987800, impactt@muko.info

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 June 2017
Global end of trial reached?	Yes
Global end of trial date	27 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is 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.
The objective to prevent infections with PA is also to diminish the need of antibiotics and minimize the problem of bacterial resistance against antibiotics.

Protection of trial subjects:

Since eggs represent normal dietary components there is practically no risk of toxic side effects of IgY. Accordingly, adverse reactions have never been detected so far. Regarding the assessment of the immunogenic potential of IgY which - under theoretical
considerations - might reduce treatment efficacy by the induction of human anti IgY antibodies, it is important to stress that IgY is not immunogenic in humans, when it is given orally (Larsson et al 1991). Patients with history of allergy/hypersensitivity to hens' egg proteins (including medication allergy) that is deemed relevant to the trial by the investigator are excluded from the trial. "Relevance" in this context refers to any increased risk of hypersensitivity reaction to trial medication. Clinically relevant diseases or medical conditions other than CF or CF-related conditions that, in the opinion of the investigator, would compromise the safety of the patient or the quality of the data are an exclusion criteria as well. This includes, but is not limited to, significant hematological, hepatic, renal, cardiovascular, and neurological diseases
(diabetic patients may participate if their disease is under good control prior to inclusion). Patients who are pregnant cannot be included into the study. This will be tested at inclusion visit with a urine pregnancy test (in female patients older than 10 years
with secondary sexual characteristics) Insurance coverage is provided by Atrialis GmbH and Elscher Consulting respectively as stipulated by law, for all patients enrolled in the study from the time of patients„ inclusion into the study. This insurance covers any damage to health arising from participation in the study up to maximum sum required by law.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Austria: 9

Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Germany: 70
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Ireland: 9
Country: Number of subjects enrolled	Italy: 13
Worldwide total number of subjects	164
EEA total number of subjects	164

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	100
Adolescents (12-17 years)	39
Adults (18-64 years)	25
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 47 sites in Germany, Belgium, Ireland, Sweden, Hungary, Poland, Austria, Italy and Spain.
Patient recruitment took place from November 2011 to June 2015.
first patient screened: 14NOV2011
first patient included: 29NOV2011
last patient included:

Pre-assignment

Screening details:

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 3 years that had been eradicated at the time of inclusion into the study.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Verum

Arm description:

IgY gargling solution
Avian polyclonal anti-pseudomonas antibodies (IgY), 70 ml gargling solution contains 50 mg IgY with an activity against PA, once daily.

Arm type	Experimental
Investigational medicinal product name	avian polyclonal IgY antibody against Pseudomonas aeruginosa
Investigational medicinal product code	Anti-Pseudomonas IgY
Other name	
Pharmaceutical forms	Gargle
Routes of administration	Oromucosal use

Dosage and administration details:

Gargling of 50 ml solution per day at night after teeth brushing before bed, containing
50 mg of Anti-Pseudomonas IgY with an activity of > or = 5 FKU (Fresenius Calvi units) / ml
ELISA unit / ml enzyme-linked immunosorbent assay unit / millitre

Arm title	Placebo

Arm description:

Avian gargling solution containing unspecific IgY antibody as Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo with unspecific anvian polyclonal IgY antibodies
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gargle
Routes of administration	Oromucosal use

Dosage and administration details:

gargling of 50 ml placebo solution per day at night after teeth brushing before bed.

Number of subjects in period 1	Verum	Placebo
Started	83	81
Completed	83	81

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description:

REMARK: A total of 171 patients were randomized to placebo (n=86) or to treatment (n=85).
From the 86 patients allocated to placebo, only 81 received intervention, 5 patients declined to participate before receiving the intervention.
From the 85 patients allocated to treatment, only 83 received intervention, 1 patient declined to participate before receiving the intervention and 1 patient had a PA infection before receiving the intervention. These 7 patients who dropped out before receiving intervention were not included in the database of the study and therefore were not considered in this report.
In conclusion the overall trial reporting group of 164 subjects consists of 81 patients of the placebo group and 83 patients of the treatment group.

Reporting group values	overall trial	Total	
Number of subjects	164	164	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	100	100	
Adolescents (12-17 years)	39	39	
Adults (18-64 years)	25	25	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	82	82	
Male	82	82	

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

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 randomisation.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

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.

Reporting group values	Full analysis set	Safety population	
Number of subjects	164	164	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	100	100	
Adolescents (12-17 years)	39	39	
Adults (18-64 years)	25	25	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	82	82	
Male	82	82	

End points

End points reporting groups

Reporting group title	Verum
Reporting group description:	

IgY gargling solution
Avian polyclonal anti-pseudomonas antibodies (IgY), 70 ml gargling solution contains 50 mg IgY with an activity against PA, once daily.

Reporting group title	Placebo
Reporting group description:	

Avian gargling solution containing unspecific IgY antibody as Placebo

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	

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 randomisation.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	

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.

Primary: Time_to_Infection

End point title	Time_to_Infection
End point description:	

The confirmatory analysis of the primary endpoint was performed for the FAS. Additional efficacy analyses were conducted for the PP-population.
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, a Cox Regression was performed with the Group Treatment adjusted by history of PA, Gender, Age (children/adults) and FEV (greater/smaller than median).

End point type	Primary
End point timeframe:	

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

End point values	Verum	Placebo	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	83[1]	81[2]	164	
Units: days of gargling				
number (not applicable)	83	81	164	

Notes:

[1] - n=1 declined to participate.
n=1 infection before received mediation.
[2] - (n=5) declined to participate.

Statistical analyses

Statistical analysis title	Statistical analysis of the primary endpoint

Statistical analysis description:

The primary efficacy endpoint is analysed using a log rank test. The null hypothesis is that there is no difference in time to recurrence of PA in the sputum of active treatment and placebo, respectively. The alternative hypothesis is that the active treatment is superior. Superiority of IgY will be claimed if the p-value from the comparison is < 0.0464 at the final Analysis (an Interim Analysis was planed with a p-value smaller than 0.0115).

Comparison groups	Verum v Placebo
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9469
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.215
upper limit	34.55

Secondary: FEV1

End point title	FEV1

End point description:

Change of the FEV1 values over time.

End point type	Secondary

End point timeframe:

Period from baseline to end of study, where data have been collected at planned visits every 13 weeks.

End point values	Verum	Placebo	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	83	81	164	
Units: Forced Expidatory Volume in 1 sec				
number (not applicable)	83	81	164	

Statistical analyses

Statistical analysis title	Statistical analysis for FEV1

Statistical analysis description:

A preliminary longitudinal analysis was performed with a linear mixed effects model using classical techniques. This analysis shows that the data contains outliers and the assumption of normally distributed residuals was violated. For this reason, we developed a full Bayesian analysis which relaxes those model's assumptions. In addition, this model is robust against outliers. The conclusions of this statistical analysis are based on the Bayesian analysis.

Comparison groups	Verum v Placebo
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Slope
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	0.001

Secondary: Number of Exacerbations

End point title	Number of Exacerbations

End point description:

This is a comparison of the number of exacerbations between the treated groups.
An exacerbation will be defined as change in at least two of the following signs:
1. Change in sputum volume or colour
2. Increased cough
3. Increased malaise, fatigue or lethargy
4. Anorexia or weight loss
5. Decrease in pulmonary function by 10% or more /Radiologic changes
6. Increased dyspnoea

End point type	Secondary

End point timeframe:

The total number of exacerbations, from screening visit to end of study counted for each patient.

End point values	Verum	Placebo	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	83	81	164	
Units: number of exacerbations	83	81	164	

Statistical analyses

Statistical analysis title	Analysis of the number of exacerbations

Statistical analysis description:

A Poisson regression model was planned for analysis but it was not appropriate to explain the data. The Residual Deviance was larger than the number of degrees of freedom. Therefore, we cannot rely on the results of this model. Conclusions are based on the Negative Binomial regression model, which fitted the data better (the residual deviance was smaller than the degrees of freedom).

Comparison groups	Verum v Placebo
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.36
Method	Negative Binomial regression
Parameter estimate	Log odds ratio
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.23
upper limit	0.46
Variability estimate	Standard error of the mean
Dispersion value	0.421

Secondary: Days of illness in hospital

End point title	Days of illness in hospital

End point description:

This is a comparison of the number of days in hospitals between the treated groups.

End point type	Secondary

End point timeframe:

The total number of days in hospital, from screening visit to end of study counted for each patient.

End point values	Verum	Placebo	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	83	81	164	
Units: days in hospital	83	81	164	

Statistical analyses

Statistical analysis title	Statistical analysis of days in hospital

Statistical analysis description:

A Poisson regression model was planned for analysis but it was not appropriate to explain the data. The Residual Deviance was larger than the number of degrees of freedom. Therefore, we cannot rely on the results of this model. Conclusions are based on the Negative Binomial regression model, which fitted the data better (the residual deviance was smaller than the degrees of freedom).

Comparison groups	Verum v Placebo
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.9
Method	Negative Binomial regresssion.
Parameter estimate	Log odds ratio
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.57
upper limit	1.31
Variability estimate	Standard error of the mean
Dispersion value	0.6525

Notes:

[3] - A Negative Binomial regression model is applied, where treatment group effect is adjusted by gender and age at baseline (children/adults).

Secondary: Days out of school or work (sick leave)

End point title	Days out of school or work (sick leave)

End point description:

This is a comparison of the number of days out of school or work between the treated groups.

End point type	Secondary

End point timeframe:

The total number of days (sick leave) out of school or work, from screening visit to end of study counted for each patient.

End point values	Verum	Placebo	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	83	81	164	
Units: days not in school/work	83	81	164	

Statistical analyses

Statistical analysis title	Statistical analysis for days out of school/work

Statistical analysis description:

A Poisson regression model was planned for analysis but it was not appropriate to explain the data. The Residual Deviance was larger than the number of degrees of freedom. Therefore, we cannot rely on the results of this model. Conclusions are based on the Negative Binomial regression model, which fitted the

data better (the residual deviance was smaller than the degrees of freedom).

Comparison groups	Verum v Placebo
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.211
Method	Negative binomial regression
Parameter estimate	Log odds ratio
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.265

Notes:

[4] - A Negative Binomial regression model is applied, where treatment group effect is adjusted by gender and age at baseline (children/adults).

Secondary: Days of use of antibiotics treatment

End point title	Days of use of antibiotics treatment

End point description:

This is a comparison of the number of days of use of antibiotics between the treated groups.

End point type	Secondary

End point timeframe:

The total number of days of use of antibiotics, from screening visit to end of study counted for each patient.

End point values	Verum	Placebo	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	82[5]	79[6]	161[7]	
Units: days of antibiotic treatment	82	79	161	

Notes:

[5] - Missing information from one patient.

[6] - Missing information from two patients.

[7] - Missing information from three patients.

Statistical analyses

Statistical analysis title	Statistical analysis of use of antibiotics

Statistical analysis description:

A Poisson regression model was planned for analysis but it was not appropriate to explain the data. The Residual Deviance was larger than the number of degrees of freedom. Therefore, we cannot rely on the results of this model. Conclusions are based on the Negative Binomial regression model, which fitted the data better (the residual deviance was smaller than the degrees of freedom).

Comparison groups	Verum v Placebo

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.52
Method	Negative Binomial regression.
Parameter estimate	Log odds ratio
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57
upper limit	0.29
Variability estimate	Standard error of the mean
Dispersion value	0.217

Notes:

[8] - A Negative Binomial regression model is applied, where treatment group effect is adjusted by gender and age at baseline (children/adults).

Secondary: BMI

End point title	BMI

End point description:

Change of the BMI values over time.

End point type	Secondary

End point timeframe:

Period from baseline to end of study, where data have been collected at planned visits every 13 weeks.

End point values	Verum	Placebo	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	83	81[9]	164	
Units: kg/m2				
number (not applicable)	83	81	164	

Notes:

[9] - 81

Statistical analyses

Statistical analysis title	Statistical analysis of BMI

Statistical analysis description:

A preliminary longitudinal analysis was performed with a linear mixed effects model using classical techniques. This analysis shows that the data contains outliers and the assumption of normally distributed residuals was violated. For this reason, we developed a full Bayesian analysis which relaxes those model's assumptions. In addition, this model is robust against outliers. The conclusions of this statistical analysis are based on the Bayesian analysis.

Comparison groups	Verum v Placebo

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Slope
Point estimate	0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.001
upper limit	0.007

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From inclsuion visit to End of study visit(Termination), plus a follow-up period for SAEs of 30 days after termination for each patient.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	4

Frequency threshold for reporting non-serious adverse events: 5 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: A total number of 1972 AEs was documented, 987 were in the placebo group and 980 in the treatment group. o deaths occurred. 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. 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.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2011	Protocol Version 1.3: Definition of chronic PA-infection concretized Exclusion criteria concerning atypic mycobacteria were defined more precisely change in frequency of sample shipment to central laboratory
20 April 2012	Protocol version 1.4: deletion of precitpitine value >/= 1 as an inclusion criteria, as this is no concrete hint for an acute PA infection. deletion of inclusion criteria "At inclusion no chronic infection with other gram-negative bacteria such as B. cepacica, S. maltophilia & A. xylosoxidans - or atypical mycobacteria or Aspergillus fumigatus" because it might be misleading in regard to one of the exclusion criteria which includes this aspect already.
13 January 2014	Amendment Protocol version 1.5; Longer stability data of the IMP from 12 months to 24 could be shown. Protocol, Investigator brochure and patient information was adapted to updated IMPD. Exclusion criteria infection with other gram-negative bacteria was defined more precisely including only those gram-negative infections were medication with PA-effective antibiotics is neccessary.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported