Immunoglobulin IgY pseudomonas A clinical trial for cystic fibrosis treatment

Executive Summary:
IMPACTT was supported by the European Union Seventh Framework Programme. IMPACTT started on January 1st 2011 as a collaboration between ten partners from seven European countries: Sweden, Germany, Denmark, Belgium, France, Italy and Lithuania. The project has since expanded to include other countries which were financed by a Swedish National Grant and the ECRIN I-A grant in 2013 and 2014. The project's primary goal was to provide an intervention therapy for prophylaxis and treatment of P. aeruginosa (PA) infections in CF patients. Anti-Pseudomonas IgY, the drug candidate, has an Orphan Drug Designation (European Medicines Agency (EMA), September 2008), and the project would provide technical data for an Orphan Drug registration for the avian antibody-based Drug Candidate Anti-Pseudomonas IgY. This technical data is a requirement for marketing authorization and for making the treatment available for CF patients within EU. The IMPACTT Project Coordinator is Professor Anders Larsson, at the Uppsala Academic Hospital in Sweden (phone: +46 18 611-4271; Email: anders.larsson@akademiska.se). The Clinical Study Sponsor is Mukoviszidose Institut (MI) whose Scientific Manager, WP2 leader and Global Project Manager for Anti-Pseudomonas IgY (also referred to as PsAer-IgY) (GPM), is Dr. Jutta Bend (email jbend@muko.info or phone: +49 228 98780-47).

The clinical phase III study investigated the critical preventive and therapeutic effects of anti-Pseudomonas IgY in CF patients, by assessing the time to reinfection with PA after successfully treated acute or intermittent infection. The primary endpoint is the time to re-infection with PA. The samples are analyzed in the Central Lab in Copenhagen (Prof. Niels Høiby's group) throughout the clinical study. Anti-Pseudomonas IgY is the Drug candidate under investigation in all the IMPACTT work packages (WPs). IMPACTT has eight WPs, which supported either pre-clinical or clinical research.

The chore part of IMPACTT, the pan-European clinical trial phase III, is headed by the Sponsor MI, WP2 leader. WP2 provided the infrastructure necessary for the clinical trial and ensured that the clinical study (ClinicalTrials.gov Identifier:NCT01455675) is performed...
efficiently, with highest quality and according to GCP and the national and international regulations. Its goal was to investigate the recurrence of PA in the sputum of the patients who gargle with Anti-Pseudomonas IgY or a placebo formulae for two years. The clinical trial recruited 164 patients from 9 European countries: Germany, Sweden, Italy, Belgium, Ireland, Poland, Hungary, Spain, and Austria. The five newest countries were added with an Amendment to the EC GA in 2013. The project was prolonged by an amendment II to the EC Grant Agreement on 2014-12-09, by two years. The recruitment was closed June 2015. The clinical study has been registered in the international clinical trial registry clinicaltrials.gov.

The IMPACTT project mobilized the critical mass of experts from academia, patient organizations, clinical trials managers, clinicians and industry. The clinical trial is built on multiple synergies: those between CF-clinical trial sites across Europe and those with clinical competence networks both nationally and on a European level; both inside and outside of the Consortium. In such, the clinical trial Partners include Contract Research Organizations that are members of the European clinical research infrastructures Network - ECRIN. These CRO affiliates are nationally established, in terms of national “management centres”. The Medical Faculty of the Heinrich-Heine University Düsseldorf (Partner UDUS), of which the Coordination Centre for Clinical Studies (KKS) is a core unit, acted on behalf of the European Clinical Research Infrastructures Network (ECRIN). Added competence to bridging the academic world and industry is given by MI. MI is involved in the CF specific clinical trial network ECFS-CTN (established within a Framework-6 project (EuroCareCF) and coordinates the national clinical trial network CF-CTN Germany. The experience of MI gained within the EuroCareCF-Workpackage on small and medium-sized enterprises continuously helps to optimize the collaboration with the SME Partner Immunsystem AB.

Project Context and Objectives:

The objective of the IMPACTT project is to provide an oral immunotherapy based intervention therapy for prophylaxis and treatment of P. aeruginosa infections in patients with Cystic Fibrosis and to make this treatment available for the treatment of CF-patients worldwide.

Cystic Fibrosis (CF) is a severe inherited disease with premature death characterised by progressive obstructive pulmonary disease. Cystic Fibrosis is the most frequent life threatening genetic disease in Europe, with around 40,000 patients. In some countries, the median age of death of people with Cystic Fibrosis is more than 35 years while in others, the majority die during childhood. Eighty percent of all CF patients are infected with the gram-negative bacterium Pseudomonas aeruginosa (PA) and by the age of 18 a majority of the CF patient population is infected with PA. Although early PA infections are possible to eradicate with heavy doses of antibiotics, repeated PA infections will occur, leading inevitably to a chronic state. When the infection becomes chronic, PA is practically impossible to eradicate by antibiotics. Chronic pulmonary infection with PA leads to a more progressive decline in pulmonary function, which is the leading cause of morbidity and mortality in CF patients. It also leads to a heavy use of antibiotics to treat exacerbations of PA infections. PA cultures from CF patients are more resistant to antibiotics than cultures isolated from other patient groups. It is thus especially important to the CF community to find effective alternatives to the current antibiotics.

Immunsystem AB (Partner 2, ‘IMS’)) developed avian antibodies against Pseudomonas aeruginosa (=Anti-Pseudomonas IgY), which received Orphan Drug Designation by the EMA (ref. no. EU13/08/56). The active ingredient in Anti-Pseudomonas IgY is a water-soluble extract from the egg yolk of hens that have been vaccinated with PA. The egg yolk (containing the IgY) from these hens is diluted in water, after which the IgY fraction is collected and 70 cc of the solution is bottled. No other ingredients are added. The patient gargles with the solution every night. IgY activity against PA is present in saliva and oro-pharynx overnight and prevents PA from entering the lungs.

A previous phase Clinical studies have shown that Anti-Pseudomonas IgY, prevents recurrent and chronic infections with PA in CF patients with total absence of adverse events. A single daily gargle with a solution of Anti-Pseudomonas IgY can postpone infections and keep the patient in good health. Furthermore, these patients require fewer courses of antibiotics. Although the active substance does not have market authorisation in the European community, Swedish CF-patients have been granted license for prophylactic treatment with the drug on a named-patient basis by the Swedish MPA.

The IMPACTT project explores the state-of-the-art of yolk immunotherapy; and moves beyond basic research on oral immunotherapy with yolk antibodies into a pharmaceutical treatment that will benefit the Cystic Fibrosis community within the EU and worldwide. To do this, we conduct a prospective randomized, placebo-controlled, double blind, multi-centre study (phase III). We are also evaluating clinical efficacy and safety of avian polyclonal Anti-Pseudomonas IgY in prevention and treatment of recurrence of PA infections in CF patients in order to get the drug registered. Parallel to this, further in vitro studies will be performed to demonstrate mode of action and animal studies to provide data on safety and toxicity of the product.

The IMPACTT project comprised eight workpackages.
The overall goal for the pre-clinical WP1 was to technically develop the present Anti-Pseudomonas IgY formulation so it fulfills the EU requirements for an Orphan Drug. This WP is an important contributor to the translation of the project into a treatment available for the EU community. WP1 objectives were therefore to (1) optimize the present Anti-Pseudomonas IgY formulation; (2) study the effect of the formulation on bacterial growth in vitro and in vivo studies; (3) improve our understanding of the application of avian antibodies for oral immunotherapy both for the specific product, but also for yolk antibodies in general. WP1 was led by Partner Immun System I.M.S. AB (IMS).

The objectives for the Clinical Study WP2 was to provide the infrastructure necessary for the clinical trial and ensure that the clinical study is performed efficiently, with highest quality and according to GCP and the national and international regulations. WP2 was led by Partner MUKOVISZIDO INSTITUT - GEMEINNÜTZIGE GESELLSCHAFT FUR FORSCHUNG UND THERAPIEENTWICKLUNG (MI).

Work package 3 assessed the primary clinical end-point which is: time from start of treatment (=Day 0) to the first recurrence of PA (Pseudomonas aeruginosa) in the sputum or throat cough swab. The other objective of the WP was to assess the secondary clinical endpoint: to measure serum pseudomonas (PA) antibodies (=precipitins) in serum. In addition to confirming that no intermittent or chronic infection has been missed, MOA studies investigated the manner by which the drug ‘Anti-Pseudomonas IgY’ may prevent reoccurrence of PA in the lungs.

The precipitin tests were only performed at the centralized laboratory as this is a specialized test that is not widely available across Europe. The precipitin test is primarily a marker for chronic PA infections. Normally it is considered as a marker for chronic PA infections in the lungs, but may also be due to an immune response to PA infections in other organs. Precipitins is thus less specific for pulmonary PA infections than the sputum culture. This is the reason for sputum cultures, but not precipitins, were used as primary endpoint. The occurrence of precipitins is an important sign that there may be PA lung infections and according to the study protocol the precipitins should be used as part of the patient evaluation at the point of inclusion. Both sputum cultures and precipitins are used in the final analysis of the efficacy of the treatment. WP3 was led by Partner 4 REGION HOVEDSTADEN (RH).

The objectives of WP4 was to identify modes of action of Anti-PA antibodies during oral immunotherapy, and (as a result) provide technical data for an Orphan Drug registration for making the treatment available for CF patients within EU. UU objectives were therefore to perform: 1) perform human pharmacokinetics studies, that studied the duration of specific antibodies in the oral cavity in CF patients, 2) bioavailability studies, to identify if there are any antibodies against anti-Pseudomonas IgY (Anti-IgY) produced in the serum of anti-Pseudomonas IgY treated patients, as such a response could reduce the effect of the treatment; 3) A human efficacy study; to study the effects of the Orphan Drug treatment on the inflammatory activity in clinical trial patients WP4 was led by Partner Uppsala University (UU). Since an infection with PA will cause an inflammatory response, a reduction in the infectious load should reduce the inflammatory response. This possible mode of action will be evaluated by measuring the well-established inflammatory marker hsCRP in the patients included in the clinical trial.

The objectives of WP5 was to provide important animal toxicity data for the translation of the Orphan Drug into a treatment valuable the EU community. The results of this WP will help develop future oral immunotherapies against microorganisms in both humans and animals. This WP is essential for an EMA approval for marketing the orphan drug and for the translation of the RTD results to a pharmaceutical preparation. All the deliverables in the WP will be used for the orphan drug registration.WP5 was led by Partner VALSTYBINIS MOKSLINIŲ TYRIMU INSTITUTAS INOVATYVIOS MEDICINOS CENTRAS (VU).

The objectives of WP6 was to produce the anti-Pseudomonas formulation for the clinical study. This WP was crucial for the translation of the project into a treatment available for the EU community. For this, IMS coordinated the egg production, immunization of the hens, and collection of eggs from high responding hens; produced GMP and MPA approved formulations containing specific anti-Pseudomonas antibodies and placebo controls. WP6 was led by Partner IMS.

The objectives of WP7 was to build a platform to support meaningful involvement for CF patients in clinical trials in the future. The sum of this WP was to motivate compliance of the patients; promote an increased public awareness of the clinical research; disseminate the findings of this investigation and to provide a comprehensive understanding of the trial conduct and its results. WP6 was led by Partner CYSTIC FIBROSIS EUROPE EV.

The objectives of WP8 was to set and maintain the organisation of the project, including management routines for the activities, and to make sure that the routines are applied by all beneficiaries throughout the project duration, to create optimum conditions for progress.
The details of the project organisation and management routines were defined in the Consortium Agreement, and EC Grant Agreement. WP8 was led by Partner UU.

**Project Results:**

The official start date of IMPACTT is January 1st, 2011. The clinical trial (WP2) is the main part of the IMPACTT project but we also have preclinical (WP1, 3, 4, 5), dissemination/patient representation (WP7), and management (WP8) parts that all are of importance for the success of the project. The project also has a work package for the anti-Pseudomonas formulation production for the clinical study (WP6).

The IMPACTT clinical trial infrastructure was set up in the first reporting period, for regulatory and ethical approvals, in this multinational clinical study, a two-step procedure was chosen. In a first step approval was sought in Germany. Thereafter approval was aimed at in the other participating countries (Italy, Belgium, Sweden, and France). A sequential instead of the VHP-procedure (Voluntary Harmonization Approach) approach was taken to try to eliminate protocol variations between countries.

The first patient was included in Germany in November 2011. In the beginning of the second reporting period we started successively including patients in Sweden, Belgium and Italy. In response to the slower than expected recruitment rate we had during period 3, we expanded the study into Ireland, Spain, Hungary, Poland and Austria. By the end of this period we also started to include patients in Ireland and were in the application/start up phases in Spain, Hungary, Poland, and Austria. We also increased the number of sites in the countries where the project is actively recruiting patients, and made enquiries to CF patient organizations, and CF centres to see how we can improve the patient information in our study (and patient information in general) to improve recruitment. Both the clinical trial Sponsor and CF Europe have been actively engaged in contacting the centres to join the study. This significantly improved the recruitment rate and by June 2015 we had included all patients needed for the study and stopped recruiting.

Real-time storage of GMP doses at ≤ -15°C (up to 24 months), +4°C (up to 5 weeks) and +20°C (up to 3 weeks) indicates that the potency and microbiological quality is unaffected. This shows that the antibody preparations are stable. This is important information, as the patients will sometimes store the antibody formulation differently from the specification. The antibody formulation also retained the activity after repeated freezing and thawing cycles. From a standpoint of potency, the medication can be handled outside of the recommended storage at ≤ -15°C. This gives the possibility of dramatically simplifying the logistics for the product under a marketing authorization. Because of new stability data (mainly prolongation of expiry date justified by most recent long-term stability testing), IMPD was been updated in October 2013. Study protocol (version 1.5 2013_10_17), IB and patient related documents had to be adapted accordingly. This latest amendment was submitted to the competent authority and Ethic Committee on December 5, 2013. This update has facilitated the logistics of drug supply and made the handling for patients easier.

WP1

Partners IMS, UU and RH have mainly performed the WP1 work. The purpose of the WP was to gather information on the stability of the IgY solution, study the reactivity of the antibodies against PA strains and effects of the antibodies on pseudomonas bacteria, and explore the possibility of future drug formulations that are more convenient for the patients.

Significant results are the positive results from the stability tests and the corresponding stability of the freeze-dried powder. In the short-term this provides the possibility to extend the shelf-life to 24 months, and in the long-term it shows that the complete development towards a different formulation should be feasible.
were investigated, including some of the antigens used for immunization. Anti-Pseudomonas IgY was shown to be immunoreactive against all of them which also included some mucoid strains. This strengthens the potential of Anti-Pseudomonas IgY as a prophylactic treatment against PA.

WP2

Setting up a multicentre clinical study is very complex. The study protocol was prepared in collaboration with the CF patient organisations and the European CF clinical trial network. For regulatory and ethical approvals, a two-step procedure was chosen. An approval was first sought in Germany; thereafter approval was aimed at in the other participating countries (Italy, Belgium, Sweden). In addition, a sequential approach (instead of the VHP-procedure, 'Voluntary Harmonization Approach') was taken to eliminate protocol variations between countries. Germany, with its excellent organization of the cystic fibrosis network, and a good existing clinical trial infrastructure, achieved the regulatory/ethics approval in the anticipated project timeframe.

The application in Germany was submitted late summer 2011, and the recruitment in a substantial number of sites started early. Due to the complexity of the approval procedure and the trial set up, input from the German experience was used to optimize the procedures in the other countries. The results of the German approval process were fed into preparation work of the other countries and experiences with the complex logistics of the clinical trial (e.g. handling of medicinal product) transferred to the other countries.

In period One, the first patient was included in Germany in November 2011. The set-up of the clinical infrastructure including the essential trial documents, the role definitions and the study management software were in place. By 18 months the trial was successfully launched in Germany after having met the regulatory requirements. Other countries (Belgium, Sweden, Italy) soon followed. In period two, we were recruiting patients in Germany, Belgium, Sweden and Italy. The MPA and ethical approvals were only the first steps in a clinical trial. Each centre had to be trained, inspected and approved for the specific clinical trial before it could enrol patients.

At the end of period two we had enrolled and included 80 patients. This was close to 50% of the 180 patients that is planned for the study, and it is over 50% of the minimum number of patients required according to the statistical analysis before the initiation of the study (144 patients). This is the minimum number of patient required if there are no drop-outs in the study. The number of drop-outs is difficult to predict in advance, but it was calculated that it would not be more than 36 in the IMPACTT study (144+36=180). The rate of recruitment was improving steadily over time and would improve even further during the next year. With the continuing recruitment in the initial countries, and with the predicted addition of new countries, we expected to have completed the enrolment of the patients during the second half of 2014.

In period two we started a patient recruitment in Ireland, during which four additional countries were approached. After the final approval from the authorities and ECs in Austria, Spain, Hungary, and Poland, recruitment in the last four countries started Q2 and Q3 of 2014. We also increased the number of sites in the countries where the project was already actively recruiting patients.

In summary, the trial concept worked by the end of period two, and the trial was very likely to produce a meaningful result answering the research question provided.

Due to the initial slow recruitment rate, and in an effort to spur recruitment, we made inquiries to CF patient organizations and CF centres to investigate how we could improve the patient information, and therefore patient involvement in our study. In this effort, both the clinical trial Sponsor and CF Europe were actively engaged in contacting centres to join the study. This action significantly improved the recruitment rate and by June 2015 we had included all patients needed for the study. We never stopped until our recruitment goal was met.

The IMPACTT clinical trial infrastructure was set up in good quality and proved to be both appropriate and sufficient for conducting the trial. Enrolment of patients were finalized successfully in reporting period 3 (which could be confirmed by the data available in reporting period 4). 164 patients were enrolled into the clinical trial. 144 data sets are sufficient from a statistical point of view to eventually analyze the data and yield valid evidence for or against efficacy of anti-Pa-IgY. By the end of December 2016, 125 data sets were achieved.

The IMPACTT clinical study has been ongoing for five years, and there still has not been any serious adverse event linked to the study medication. Thus, still there was no severe adverse reaction of the drug detected. The annual checks of more comprehensive safety data did not reveal any safety issues either. The number of drop-out patients remains at a very low rate which is lower than actually
A quality management concept was established in period 1. It was adapted in reporting period four and is followed until the end of the trial. More than 10 audits as well as more than 20 qualification visits and co-initiation visits have been performed to ensure quality and GCP-compliance of the trial participants. In reporting period 4, within the new risk-based quality management 20 of the 60 Monitoring reports have been checked as a random sample and analysed regarding any new risks. There were no risks identified that were more than low, so no new audit was scheduled and conducted.

The planned unblinded interim analysis is currently ongoing and will be finalized in March 2017. Therefore, there were no changes in study design, and the decision was taken to finalize the trial as planned. There will be another opportunity to analyse for efficacy after the remaining patients have finished the study also. We offer to give an update report on this in January 2018 to EU (the interim analysis which will be available in March 2017 and final analysis which will be available in Jan. 2018).

WP3
Pre-clinical work
The main pre-clinical work focused on the effect of anti-pseudomonas IgY on the killing of pseudomonas bacteria. The in vitro studies clearly demonstrated that anti-Pseudomonas IgY opsonizes PA and enhances the successive bacterial killing by phagocytic cells (PMNs and macrophages). The presence of anti-Pseudomonas IgY antibodies alters the innate immune response and induces a faster bacterial clearance due to augmenting the phagocytic activity of PMNs and macrophages. Blocking the Fc-receptors on the surface of PMNs phagocytizing IgY opsonized PA did not alter the phagocytic activity, suggesting a non-Fc receptor mediated interaction between IgY antibodies and PMNs. The IgY antibodies opsonize PA that forms aggregates that are readily phagocytized by PMNs, implying a mode of action to the possible clinical impact of oral immunotherapy with anti-PA IgY.

We have also shown that anti-Pseudomonas IgY effectively reduces the number of bacteria in the lungs in a murine model of acute pneumonia. This was achieved without any adverse events. Thus, it seems possible that IgY antibodies could be used in the future to treat pulmonary infections. The use of such treatment in humans is however beyond the scope of the IMPACTT project. Yet, these discoveries have recently laid the foundation of second project that is currently testing the positive effects of anti-Pseudomonas IgY and other anti-MDR bacteria IgY formulations in pigs in a VAP model (see: SWEASCI project).

Both the project's in vitro and in vivo studies are important additions to our understanding of the mode of action, and both parts will be used as part of the orphan drug application. The results of the pre-clinical work have been published in scientific journals, and the WPs combined findings led to a PHD thesis by Dr. Kim Thomsen.

Clinical work
WP3 is also part of the clinical study. The clinical analysis work included identification of PA in the sputum cultures (primary end-point) and measurement of the serum levels of precipitins (secondary endpoint). This work continues throughout the clinical study and is thus ongoing. The studies in this WP were performed successfully, and followed the original time plan.

At the end of the fourth period 124 patients had been tested > 2 times which means that they have concluded the study either because they have reached the 2-year treatment point or had had a positive PA infection. Results show that 57 patients had precipitin levels above normal range, 82 patients had PA levels above normal range. The laboratory continues doing the above analysis until the last patient in the study has concluded the study. This will be in June 2017 if this patient does not get a PA infection before this time. In such an event the laboratory work will end at this time.

The results on analysis of primary end-point and Safety show so far that we have been able to avoid including patients that were PA positive in the study. This figure is in line with the initial calculations that approximately 50% of the patients would get a pulmonary PA infection during the treatment period.

As the study is blinded so we cannot say which of the individuals have taken active anti-PA IgY's substance and which have taken the placebo treatment. A report will be submitted in early 2018, in which the un-blinded results will be presented and addressed. The Coordinator will send this report, with permission, to the project PO within one year of submitting the Final Report.

WP4

In period one, the results show that the duration of the antibodies in the oral cavity is somewhere between 8 and 24 hours, and this verifies the conclusion drawn in 2002 from the same study in healthy volunteers. Future work could be geared at increasing this window to last the full duration between the doses, but the importance of this is not known since it is stipulated that the infection occurs predominantly during the night. Before this reformulation of the medication, or before a new treatment schedule is implemented, more work should be done around the infectious route and the timing of infection. Until more information is available, it appears that the current treatment is well fitted for its purpose. The low median CRP value in this study is a significant finding as it shows that the patients do not have active infections at inclusion. CRP is a cardiovascular risk marker and low CRP is usually associated with a lower
risk for cardiovascular morbidity and mortality.

We also identified whether there were any antibodies against anti-Pseudomonas IgY produced in the serum of anti-Pseudomonas IgY treated patients, such as a response could reduce the effect of the treatment. These Bioavailability results show low levels of anti-chicken IgY antibodies and no signs of allergic reactions to the formulation in the clinical study. This means that the presence of anti-IgY antibodies is lower than previously reported for antibodies to various mammalian antibodies. In a previous study (Kricka, 1999) 2.9% positive samples is lower than the previously reported presence of anti-mouse IgG antibodies in humans (5-40%). Thus, we have not received any adverse events indicating an allergic reaction to the formulation. The results in agreement with the previous toxicity studies performed in animals. The study is blinded so we cannot say which of the individuals with positive titers that has been taking active substance and which individuals that has been on placebo treatment. A report will be submitted in 2017, in which the un-blinded results will be presented and addressed. The Coordinator will send this report, with permission, to the project PO within one year of submitting the Final Report.

We also did a Human efficacy study where we studied the effects of the Orphan Drug treatment on the inflammatory activity in clinical trial patients. Preliminary results from the efficacy study showed that the CRP values were generally low which verifies the basic setup of the study, that the included patients did not have pseudomonas infections at inclusion or during the initial treatment period. When the study is un-blinded we will also look at the specificity and sensitivity of CRP as an early marker for PA infections in CF patients. The sputum cultures will be used as the true marker for PA infections and the sensitivity and specificity of CRP will be calculated in relation to the sputum result (WP3).

WP5
In period 2, the preclinical studies show that the oral administration of anti-PA IgY had no effect on the normal and pathogenic bacterial mice micro flora. It also showed that the treatment did not damage the gastrointestinal tract in a mouse model.

WP6
The Anti-Pseudomonas IgY production was a success. In the initial step, all activities involving the production of active and placebo formulations for the clinical study were started, these formulations were inspected and received the Swedish MPA approval. The first produced batches from the subcontractor were bottled in May 2011, and were used for validation of the production. In addition, the ethical permits, documentation, quality control testing and contracts needed to produce the formulation were successfully completed.
In step two, we established an operational production of formulation from the egg to the patient. To do this, the production and shipment of doses had laid out a detailed logistics management. This management was coordinated by Partners UU and IMS, in close collaboration of Partners MI and UDUS. Pharmacy Mainz, a subcontract to Partner UU, performed the randomization and individual patient labelling of the doses. The Partner's management-level collaborative work also handle the shipments to the sites which was performed approximately twice during a three-month period. In the early part of the CT each patient received formula for 3 months per shipment at their visits to the CF centres. By the project third period, with the new stability data (WP1), less frequent shipment and longer storage of the Drug/placebo occurred.

A successful integration of all of the work package components was essential to achieve a controlled delivery of doses to the patients. The most significant result of the work package is that a successful end-result was achieved, that the procedures were in place before they were needed, and that supply to patients was available and secured throughout the duration of the project.

WP7
The clinical study (amongst others) included a questionnaire to search for and define methods for meaningful involvement of the patients. This questionnaire was developed by Cystic Fibrosis Europe (CFE), the Federation of 40 National European CF Associations in Europe, in a collaborative effort with the clinical trial Sponsor. The results of the survey are summarized
- Patient representatives need to be an equal partner in the project & all stakeholders need to be convinced this is the only way to come to an optimal research project.

Patients and patient representatives should be made part of a clinical study planning. All organizations promoting clinical studies should understand that patients are not the ‘objects’ of a study but are crucial stakeholders, weighing heavily in the outcome of any study. They are part of a process that is very important to put into practice. This means that clinical studies are much more successful if patient representatives are involved in the study from a very early stage. Our results show that feedback from both patient and patient representative groups are very valuable during the set up and implementation of the trial design, and are critical throughout all phases
Personal contact is key

During the study, we realized that the only way to receive good information from patients is to make them feel 'heard'. This was best be achieved by creating national study contact persons for the patients, as (due to privacy reasons) we couldn't contact them pro-actively. We found that both good communication with the patients as well as good communication with the study centers is needed for comprehensive study feedback. Our results demonstrate that if we want patients to become involved meaningfully in a clinical study, we need to make sure that also the professionals understand this. Therefore, we need to rethink the way we reach out to both types of collaboration – a key aspect for success.

Patient participation should be approached in a professional manner.

We found that any survey should be provided with sufficient budget that includes covering costs for unexpected expenses.

Patient organizations can play a major role in mediating between researchers and sponsors of the clinical trial on the one hand and the clinical trial sponsor and patients on the other.

Patient organizations are in the position to translate the scientific information comprehensibly to the patients. They can also inform the researchers of the patient's perspective, which is valuable. Patients are promoted in this way not only as the study-object, but as individuals who are critical for the completion and success of patient recruitment and of the study. In IITs (investigator-initiated trials), researchers and patients have the same goal, normally. Thus, a joint approach with the patients makes sense. We find that our successful patient communications, enrolment, low drop-out rate and a high patient adherence successfully impacted on the outcome of this clinical trial. Therefore, our patient involvement in all stages of the study, especially in the planning of a study, was a win-win situation for all. This is not specific to this study but can make a difference in each clinical trial.

Potential Impact:
Overreaching potential impact (benefit) of the project

- Improve the health of European citizens

A primary objective of IMPACTT was to make a significant contribution to CF research and improve the prognosis of CF patients. Researchers at Immunsystem AB (Partner 1) have developed avian antibodies against pseudomonas (=Anti- Pseudomonas IgY), which has received Orphan Drug Designation by the EMA (ref. no. EU13/08/56). The active ingredient in Anti-Pseudomonas IgY is a water-soluble extract from the egg yolk of hens that have been vaccinated with PA. The patient gargles with this solution for 2 minutes every night after tooth-brushing. IgY activity against PA is present in saliva and oro-pharynx overnight and prevents PA from entering the lungs. (Carlander et al, 1999). Although the exact mechanism of action is not known, our studies show that Anti-Pseudomonas IgY binds to flagellin (Nilsson et al, 2008).

Phase I Clinical studies have shown that Anti-Pseudomonas IgY, prevents recurrent and chronic infections with PA in CF patients with total absence of adverse events. A single daily gargle with a solution of Anti-Pseudomonas IgY can postpone infections and keep the patient in good health. Furthermore, these patients require fewer courses of antibiotics (Nilsson et al, Paediatric Pulmonology, 2008, 43:892). Although the active substance does not have market authorisation in the European community, Swedish CF- patients have been granted license for prophylactic treatment with the drug on a named-patient basis by the Swedish MPA.

Pre-clinical data from IMPACTT clearly underline that IgY is effective against Pseudomonas aeruginosa, at least when administered in mice. Those results do also indicate that unspecific IgY is effective against bacteria such as Pseudomonas aeruginosa to a lesser extent than the specific anti-PA-IgY used as drug in the clinical trial. In addition, the administration route of inhalation was also an effective option in mice.

These findings clearly increase further the probability that results from the clinical phase III trial which will be completed in Dec. 2017 will also confirm efficacy. Good Clinical Practice prohibits an unblinded data analysis unless it is planned a priori. The planned interim analyses conducted during the IMPACTT project duration gave no hint whether the drug is effective or not. However, this was not expected due to the low number of patients which was planned to be included into theses interim analyses. The interim analyses on
blinded data already showed an excellent safety profile of the IgY drug. Data from the final analyses will be available beginning of 2018 and we would be happy to provide the EC project Officer Dr Diana Salmen with a comprehensive summary of the results.

Even if the trial fails to show efficacy it will provide further documented knowledge to dramatically improve the care of patients with CF. Taking together all IMPACTTT results will lead to the possibility of further development of the IgY drug, even if the actual oral formulation and trial design could not show efficacy. Provided that the results show efficacy of IgY, the primary result of the proposed study will be a new orphan drug that will improve the health of CF patients by reducing the time to pseudomonas infection and resulting lung damage in these patients.

The natural response by humans to any infection is the production of antibodies of the IgG-class directed to systemic infections and secretory IgA directed to infections of the mucus membranes, including the oral cavity and respiratory tract. In CF, alarming drawbacks regarding antibiotics is the development of resistance by PA to the antibiotic drugs

- The production of antibodies (Abs) to IgY Abs was tested (WP 4): there was no immune reaction to oral IgY applications.
- In the European clinical trial, that stretched over 9 countries, the clinical trial data monitoring committee established that the oral treatment is safe (WP2)
- Animal experiments conclude that the treatment is safe (WP3 and 5)

We will be able to confirm anti-PA IgY as a novel safe therapeutic Drug.

Within this year, we will provide new clinical data for a new safe Drug candidate for the market that has the potential to replace antimicrobials, using an extraneous source of immunoglobulins for the prophylaxis of PA infection in CF patients. By doing this, the IMPACTTT project directly addresses the main impact statement of the Health programme which is “Improving the health of European citizens ... while addressing global health issues”.

By implementing a Europe-wide phase III clinical trial, IMPACTTT succeeded in providing a validation of a potential treatment to be used globally to treat Cystic fibrosis patients who suffer from this devastating disease. We will thus confirm the Health programme objective “the development and validation of new therapies, methods for health promotion and prevention including promotion of child health”.

- Increase and strengthen the competitiveness and innovative capacity of European health-related industries and businesses
  - by validating a novel state-of-an-art therapy, that challenges the contemporary and considerable use of antibiotics, anti-PA IgY both increases and strengthens the competitiveness and innovative capacity of European health-related industries and businesses
  - The use of a food product (egg antibodies) as a human pharmaceutical is new. It has raised questions regarding the borders between food, functional food and pharmaceuticals. This is an important innovative step towards using food products for medicinal purposes.
  - Since there are international suppliers who offer unspecific IgY as a dietary supplement on the internet, IMS develops anti-PA IgY as a defined product that is investigated regarding safety and efficacy so that patients can rely on the quality of the product. The anti-PA IgY development aims at receiving marketing authorization and reimbursement by the health insurances so that all patients who need it can benefit from the new drug.

- Future global health issues, like emerging epidemics, can be addressed in future IgY Drug implications.
  - Bacteria resistance to antibiotics is a growing global health threat with severe social and economic implications. Antibiotic use in hospitals is a major driver of the emergence and spread of multistart-resistant bacteria that are responsible for healthcare-associated infections. This is of great concern, and is a threat to patient safety in Europe where antibiotic-resistance already has made its mark in European healthcare.
    - On November 2016, Health First Europe organised a meeting of the European Parliamentary Interest Group on Innovation in Health and Social Care to discuss tackling antibiotic resistance and healthcare-associated infections.
    - An ongoing explosion of antibiotic-resistant infections continues to plague global health care. WHO led a global, multi-year campaign with the theme “Antibiotics: Handle with care” during the first World Antibiotic Awareness Week in November 2015.
    - Our approach could very well lead to the reduction of the amount of antibiotics used which (in turn) will lessen the development of antibiotic resistance. Validation of anti-Pseudomonas IgY (when used synergistically with antibiotics) will thereby help reduce the spread of antimicrobial resistance which ECDC states is “the greatest health threat in Europe”.
    - The primary cause of antibiotics resistance is the increased use of. Thus, the current antibiotics are becoming less and less
Effective. This in combination with a recent EU report stating that there are very few new antibiotics in development stages leads to the conclusion that we need to find alternative to antibiotics. Current approaches to lessening the use of antibiotics are usually vaccination programs (active immunisation) or the administration of immunoglobulins (passive immunisation) as in IMPACTT.

Benefit for citizen’s healthcare

- Citizens will benefit from the translation of the project's basic discoveries into clinical applications.
  - The project's basic discoveries (the preclinical work packages) are designed to contribute to identifying the modes of action of Anti-Pseudomonas antibodies during oral immunotherapy. This information was a primary objective, as it provides technical data for an Orphan Drug registration, a requirement for marketing authorization and for making the treatment available for CF patients within EU.
  - As the clinical trial structure has already been established, further clinical trials are much easier to run. This would also facilitate any further development of IgY, e.g. formulating and testing of other routes of administration, such as inhalation.
  - The 'basic discoveries' (ie. The pre-clinical studies so far) lend important new insights into the biological processes before re-infection with pseudomonas in CF patients and how IgY works, and will help the further developments of IgY therapies.

- The outcome of the study is critical for the development and validation of new IgY therapies.
  - The clinical study will validate a new IgY treatment and prophylaxis with avian immunoglobulins (IgY) to CF-patients.
  - IMPACTT is the result of a lasting, successful, pan-European collaboration between organizations to achieve common goals in an investigator-driven clinical investigation.
  - The expected impact of the specific call 2.4.4-1 for Clinical development of substances with a clear potential as orphan drugs stated that "The selected projects should mobilise the critical mass of expertise in order to test therapeutic approaches to rare diseases. The project has mobilised a critical mass of experts to execute the project goals. The only effective way to achieve the project goals was through a close European collaboration between Partners from 10 European countries, each having different competences, each with high level technological expertise and knowledge.
  - The broad applicability of the proposed IgY therapy is independent of the complicating factors currently associated with treatment of PA infection (antibiotic side effects, toxicity, resistance, etc). It demonstrates that new clinical applications can be developed even for infections which cannot be treated with conventional therapies due to the development of antibiotic resistance.
  - Our pre-clinical results not only benefit the CF patients by supporting the authorization of the Drug, but they provide a scientific foundation for developing new state-of-the-art IgY-based therapies. In particular, it supports the translation of avian immunotherapy to the benefit of patients with other infections – especially in the gastrointestinal tract.
  - The clinical study shows that the IgY Drug is safe. It also shows that there is no production of antibodies against IgY, which could diminish its activity.
  - The pre-clinical study show the IgY Drug is safe. In addition, anti-Pseudomonas IgY is not absorbed from the gastrointestinal tract.
  - Bioavailability studies show Anti- Pseudomonas IgY activity in the buccal mucosa during 24 hours after gargling, i.e. it has a lasting effect (overnight use; pre-clinical WP 4).

- Sustainable and efficient healthcare systems are encouraged by the outcome of the patient-near studies (WP7).
  - WP7, led by Partner CFE, aimed to ‘improve the quality of life of patients and their families by representing and defending the interests both at the start, during, and at the end of the project’. The patient-near studies lifted new approaches to involving and recruiting patients to clinical studies and demonstrated a critical role of patient involvement in early planning phase of a clinical trial. These patient-near studies found that the early involvement of patients in clinical studies can significantly improve the future quality, design, and outcome of the clinical studies.

Benefits for science by creating novel medical technologies for human health

- A successful outcome of the clinical study will use the pre-clinical and clinical data to develop new treatment strategies (other than the currently tested application) for local treatment of chronically colonised CF patients.
  - One result of a successful study outcome is the development of new oral applications of the anti-PA IgY orphan drug that was found to dramatically reduce the number of pseudomonas infections and lung damage in mice studies (WP3). This translation will not be limited to the current IgY based orphan drug but will most likely be followed by a range of new IgY based pharmaceuticals. Potential
human diseases that could be suitable for such treatments are C. albicans infections in chemotherapy treated patients, carriers of multi-resistant bacteria such as MRSA, ESBL klebsiella, ESBL-E.coli gastro-intestinal infections such as infections with rotavirus, salmonella and EHEC. Specific IgY can also prevent caries and gingivitis. There are also veterinary applications such as weaning diarrhoea in piglets.

- The anti-PA IgY formulation has also inspired the testing of new IgY formulations which is currently ongoing in pre-clinical research settings (see information on SWEASCI Project). New IgY formulations to several new MDR bacteria species are tested in vivo (pigs) through mechanical ventilation. These MDR bacteria are key bacteria that cause ventilator-associated pneumonia, common to CF disease, and deleterious to the health of a CF patient as well. Thus, our preliminary clinical studies findings were extrapolated to develop specific avian immunoglobulins (IgY) products for use in other severe lung infections.

- The retained stability of the new formulations (such as freeze-dried anti-PA IgY formulations; pre-clinical WP 1) facilitates easier handling and development of new formulations applications (IgY drug technology).

Optimising the delivery of healthcare to European citizens

- Translation of clinical outcome into clinical practice
- One IMPACTT goal was to translate the project outcome into a treatment available for the EU community. Once marketing authorization is obtained, the drug would be directly available to provide benefit to CF patients within the EU.

- Enhanced disease prevention and better use of medicines, appropriate use of new health therapies and technologies
- In CF, anti-PA IgY significantly postpones intermittent and chronic infections with PA and thereby diminishes the use of antibiotics as well as their drawbacks. We propose that anti-Pseudomonas IgY can be used together with antibiotics when new PA infections occur. This combined treatment will provide the same effect in terms of preventing and treating PA-infections in CF-patients but with considerably less use of antibiotics.
- We also see that anti-PA IgY intervention therapy can reduce the need to use antibiotics in patients with CF; patients, which constitute a group which currently are very high consumers of antibiotics.
- By setting up the trial infrastructure of clinical trial sites from 9 European countries, the cooperation between local laboratories and the central laboratory was strengthened. Comparing of the results from local and central lab lead to discrepancies in some cases. In case of such discrepancies, e.g. when central lab identified very slow growing SCV (small colony variant) kind of Pseudomonas aeruginosa, central lab provided counselling. This lead to an improved quality of the participating laboratories regarding identifying Pseudomonas aeruginosa having also an impact on routine care.

A synergistic effect with antibiotic treatment in cystic fibrosis patients with chronic PA infection can be investigated in future clinical trials to potentially broaden the indication of anti-PA-IgY.

Benefit for industry and SMEs

- Supports industry
- Research-based SMEs are the main economic drivers of healthcare, biotechnology and medical technologies. In general, strong EU-based biomedical research enhances competitiveness of the European pharmaceutical and healthcare industries. The project supports the development of the SME partner IMS and therefore also supported bringing European products to the global market.
- At present, there are no competitive products on the market. Thus, a marketing authorization will provide increased growth for the IMPACTT Partner IMS. IgY has been available in Sweden for a small, specific group of CF-patients since 2003. The dose price was set to 400SEK (= about 40 €) which was already at that time lower than alternative treatments on a yearly basis. A yearly cost for Anti-Pseudomonas IgY treatment at €14,600/patient can thus safely be used in a market assessment. From the total patient population, about half are not chronically infected and therefore would be eligible for treatment with Anti-Pseudomonas IgY. This gives a worldwide market of approximately €730,000,000/year or within Europe €292,000,000/year.
- Within the last years ‘CF transmembrane conductance regulator ’ (CFTR)-modulators have received marketing authorization. This new class of drugs targets the basic defect in cystic fibrosis. However, these drugs are not eliminating the need for treatment of infections in cystic fibrosis patients. CFTR-modulators and IgY can be given at the same time.
- Competitive products are still antibiotics. There have been a few new products for cystic fibrosis patients with chronic Pseudomonas infection in the last years (Aztreonamlysin, Levofloxacin). However, for cystic fibrosis patients without chronic Pseudomonas infection there are very few options (inhalement of tobramycin or colistin) and new antibiotics for this patient group are hardly developed at the moment. Therefore, anti-PA-IgY is a valuable option for these cystic fibrosis patients, especially since it can be used in combination with antibiotics for the best results.
- New partnerships for continued development of the methods will benefit the project SME, IMS
- New methods have been developed on a national level through new partnerships between Uppsala University and Uppsala
Academic Hospital in a new project SWEASCI, The project began in Dec 2016, and will collect sufficient animal data for next-stage developments of novel antibiotic resistance therapies, based on the IgY formulation currently tested in the IMAPCTT clinical trial III.

UU and RH continue their investigations into the MOA of IgY.

Main dissemination activities

CFE was the contact point for clinical trial participants. The IMPACTT Partner CFE was present at all European CF Society conferences (yearly basis) throughout the project period. Each year, CF Europe organized 2 major conferences: 1) The annual meeting, linked to the ECFS conference, and 2) The South Eastern European Conference.

In:
- 2012 they took place in Dublin
- 2013 they took place in Lisbon
- 2014 they took place in Gothenburg
- 2015 they took place in Brussels and in Bucharest.
- 2016 they took place in Basel (annual meeting) and in Skopje, Macedonia (SEE CF Conference).

Project information on scientific (pre-clinical) findings were disseminated at these meetings, as well as at the American Society for microbiology ASM general meeting, Denver, Colorado, USA in 2013.

Dissemination of project results

- Project information to the patients and to the patient organizations was disseminated through presentations at seminars at meetings in the bigger CF centres and at meetings with the national CF organisations. CFE presentations (at each of its conferences) informed its members (the national CF patient organisations) about the project developments, the project findings and the project progresses (please see project participant portal for list of dissemination activities).
- Project information on scientific (pre-clinical) findings were disseminated to the public via the IMPACTT web, scientific and CF meetings, including relevant conferences and seminars. Both Rigshospitalet and UU have published impressive pre-clinical findings (please see project participant portal for list of dissemination activities). The project has produced one thesis publication.
- Future publications (such as in the Journal of Cystic Fibrosis; Paediatric Pulmonology; Uppsala Journal of Medical Sciences) will be addressed in 2018 as publication of data in scientific journals will be pursued regardless of the nature of the results of the study.
- Stability studies in the beginning of our study by IMS were communicated so as to simplify the logistics involved in the production and distribution of the product.
- Impressive pre-clinical research results by RH showed that the anti-PA IgY are able to bind to any pseudomonas bacteria entering into the oral cavity and promote the clearance of the bacteria, leading to significantly lower bacterial counts. These results have initiated a novel research project in the field of antibiotic resistance, and the development of four new types of IgY's targeting bacteria that are known to often carry multi drug resistance (MDR): PA; Staph. Aureus (methicillin-resistant): E. coli (ESBL-producing) and Klebsiella pneumoniae (ESBL-producing).
- For transparency, the phase III clinical trial has been registered in [www.clinicaltrials.gov](http://www.clinicaltrials.gov) Identifier NCT01455675 before starting the recruitment phase and these pages have been updated ever since.

Exploitation of results

- Strategy for commercialization of the treatment

  The aim is to obtain marketing authorisation of the product in Europe as a first step. The result of the clinical study will be compiled together with preclinical data to an application to EMA for marketing authorization of the orphan drug. Immunsystem AB will be responsible for the coordination of the application to EMA.

As soon as the results of the clinical study are available, Immunsystem will also start working to obtain marketing authorization US. Marketing authorization in the US will most likely require a clinical study in the US. Immunsystem is presently trying to find a pharmaceutical partner that can handle the distribution of the drug both within EU and/or in the US. As the IMPACTT phase III study is blinded we do not have any results of the clinical study until it is finalized and all the data from the centres are collected and analyzed. As we are very close to having the results of the clinical study the pharmaceutical partners that Immunsystem has contacted want to wait for the results of the clinical study. We thus do not expect to have any signed agreement with a distributor before Q3, 2017. For the moment Immunsystem has several promising contacts that will pursued as soon as we have the results of the clinical study.
• Plan the future use and development of the results obtained during the project for the use for other diseases

The primary target is to obtain marketing authorization in Europe for the prevention of pseudomonas infections in CF patients without chronic PA infection.

Another group that are at increased risk of becoming infected is lung transplanted CF patients that have been transplanted due to P. aeruginosa infections in their lungs. The pseudomonas treatment could also benefit other patient groups. We are currently starting a preclinical study with anti-pseudomonas IgY administered intrapulmonary as a new treatment for ventilator associated pneumonia (VAP). VAP is often caused by Pseudomonas infections and we have shown in a preclinical part of the Impactt study that we can treat pseudomonas infections in a mouse model with anti-pseudomonas IgY.

The next step would then be to investigate anti-PA-IgY alone and as a combination therapy with antibiotics in cystic fibrosis patients chronically infected with PA.

• Plan to maintain relevant IPR for the treatment

An orphan drug registration gives a protection similar to a patent. The duration of the protection is 8-10 years from the time of registration of the drug. In praxis the total protected time of sale is similar for a traditional patent that is usually claimed approximately 10 years before the registration as for an orphan drug registration. Also, the product is a polyclonal antibody that is much more difficult to copy in comparison with a monoclonal antibody. Thus the choice of immunogens and hens will further protect the treatment. We also plan to add new formulation patents that will further extend the IPR protection.

• Plan to secure relevant IPR for any eventual new methodologies or products that may be developed as a consequence the project, including patent searches and analysis of patentability of new formulas.

We plan to add new formulation patents that will improve the shelf-life of the product and make it more convenient for the patients, especially also for children who comprise a big group within the potential patient population. We will also investigate the possibility to patent the VAP treatment with different formulations.

• Plan to make use of the experience and contacts of the ECRIN and other networks for dissemination

We are currently working very closely with the CF patient organizations (two of them are partners in the project) to reach out to the CF community after the results of the clinical study are obtained. We are already collaborating to disseminate the information of the study and we will continue to do so. We recently presented the study at the 3rd IRDIRC conference (February 2017) to inform about this new treatment to researchers and companies working with rare diseases.

• The exploitation of the results (released in Dec 2017)

The clinical study results will be handled by the consortium Partners IMS and MI. The project CA has addressed handling the expected economic revenue that a registration and selling of the drug will generate. Here, Partner IMS heads the Consortium's exploitation team which consists of the Consortium partners IMS, MI, and CFE. CFE will provide information about the project results to the CF stakeholders across Europe.

A `final` exploitation of project results (the clinical study findings) can only be obtained when the patient data has been un-blinded. Thus, the project results will be used and disseminated after the clinical study results have been analyzed by Partner HHU, latest by in Dec 2017.

List of Websites:

For internal and external communication purposes, we have developed a web site with open and internal pages. This facilitated information flow to CF-patients and clinical trial participants as well as communication within the centre. The website was delivered on schedule and is a ‘living’ tool, regularly updated and improved.

The open website, www.impactt.eu was developed and launched in the first reporting period. This website was a tool to continuously inform patients, clinicians and other stakeholders on the IMPACTt-project and its results. It disseminated the project-information and raises awareness amongst the wider public. Here everybody can find information about the project, its goals and about the project partners. Throughout the lifetime of the project this website was regularly updated and adjusted to the needs of the stakeholders. By the midperiod four the web developed problems with editing and updating. This problem could not be remedied as the subcontractor that attended the web was not available.
An intranet for internal use was set up and launched in the first period. This is an important well-used communication tool for the partners in the project. Through this website partners share information, documents, important dates, and more which can be accessed by IMPACTT CT clinicians http://intranet.IMPACTT.eu

The CFE-websites. In addition to the project website, which is used as a dissemination tool for the project promotion and the collection of information; CFE's own, new website (www.cf-europe.eu) and the wikiCF website (www.wikicf.com) spread information on the project to the European CF community and beyond.

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