Periodic Project Report
Inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis
iABC

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Period 08/2019 – 07/2020
Reporting Period 5
Description of work - DoW v3.5 October 2019

Date of submission: 30th September 2020 – updated November 2020

Contents

Declaration of the coordinator

I, the coordinator of this project, declare that,

The periodic report submitted is in line with the obligations as stated in Article II.2.3 of the Grant Agreement:

The attached periodic report represents an accurate description of the work carried out in this project for this reporting period;

The project (tick as appropriate):

- has fully achieved its objectives and technical goals for the period;

√ has achieved most of its objectives and technical goals for the period with relatively minor deviations[1];

has failed to achieve critical objectives and/or is not at all on schedule[2]

The public project website www.iabcproject.com is up to date, if applicable.

To my best knowledge, the financial statements which are being submitted as part of this report are in line with the actual work carried out and are consistent with the report on the resources used for the project (section 6) and if applicable with the certificate on financial statement.

All participants, in particular non-profit public bodies, secondary and higher education establishments, research organisations and SMEs, have declared to have verified their legal status. Any changes or deviations have been reported under section 5 (Project Management) in accordance with Article II.3.f of the Grant Agreement.

Name of the Coordinator: .....

Date: ...../ ...../ .....

Pertel Peter

Digitally signed by Pertel Peter
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Date: 2020.09.29 17:00:41 -04'00'

Signature of the Coordinator: .....

[1] If either of these boxes is ticked, the report should reflect these and any remedial actions taken

[2] If either of these boxes is ticked, the report should reflect these and any remedial actions taken

1 Executive summary

Project rationale and overall objectives of the project

The iABC (inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis) consortium brings together world leading researchers to develop new antibiotic treatment options for people with CF and BE by sharing expertise and resources. It involves 18 academic partners and 3 EFPIA member companies across 8 countries and four pan-European networks: ECFS-CTN, EMBARC, COMBACTE CLIN-Net and COMBACTE LAB-Net. These groups combine experience with proven expertise and success in (i) antibiotic development (ii) designing and successfully leading randomized clinical trials in cystic fibrosis (CF) and bronchiectasis (BE) (iii) high-quality research on the epidemiology, detection and treatment of chronic respiratory infection in CF and BE (iv) establishing and running a data registry and clinical trials network (v) endpoint analysis. Methodological expertise includes formulation, clinical and molecular microbiology, toxicology, clinical epidemiology, PK/PD and DMPK. Their existing infrastructure provides an excellent basis for the successful achievement of the objectives of ND4BB Topic 7 IMI JU 11th call to develop novel inhaled antibiotic regimens in patients with CF and BE**.** This will address a critical bottleneck in the development of antimicrobial agents for the treatment of chronic lung infection caused by *Pseudomonas aeruginosa* (Pa) and other Gram-negative non-fermenters (GnNFs).

The Description of Work (DoW) contains activities to deliver the following objectives:

- Determine the initial therapeutic efficacy of TIP in BE patients
- Explore novel endpoints (microbiome, LCI and CT imaging) for clinical trials in both CF and BE
- Build repositories of clinical respiratory isolates and sputum biobanks for use in future research
- Develop an EU-wide prospective registry of BE in all EU and EU-associated countries to facilitate better clinical care and future research into this disease
- Develop an inhaled formulation and dispersion device for POL7080, a novel antibiotic with activity against Pseudomonas aeruginosa.
- Determine the pharmacokinetics and safety of POL7080 in CF patients and provide efficacy data.
- Evaluate the safety and tolerability of the OSCN- and LF compounds of ALX-009, separately and combined at different doses.
- Evaluate the clinical efficacy of different doses and different administration schedules of ALX-009 and the contribution of each of its compounds (OSCN/LF) when administered separately in CF patients in order to define an optimal treatment regimen.
- Determine the therapeutic efficacy of QBW251 (a CFTR potentiator) in patients with BE

Deliverables of the project

To achieve the objectives, the programme contains 11 work packages, with deliverables summarised below:

- WP1 provides the structure to manage the administrative, legal and financial aspects of the project
- WP4 supports the clinical development of TIP for patients with BE. One Phase II study of the efficacy and safety in BE patients with a history of exacerbations and chronic Pa infection will be performed.
- WP5 develops an EU-wide registry for BE patients and aims to provide comprehensive data on the epidemiology, natural history and management of BE in Europe.
- WP6 defines new and clinically relevant exploratory endpoints which can be used in clinical trials assessing the efficacy of antimicrobials and other therapeutic agents in CF and BE.
- WP7 supports the pre-clinical development of Murepavadin (POL7080) as an inhalation therapy.
- WP8 supports the clinical development of Murepavadin (POL7080) for use in patients with Cystic Fibrosis (clinical studies). A Phase Ia study of POL7080 in healthy volunteers will be performed.
- WP9 supports a Phase I study of ALX-009 in Healthy Volunteers and in CF and BE patients to determine the safety and tolerability of the OSCN- and LF compounds, separately and combined at different doses.
- WP10 supports a Phase II study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of QBW251, a potentiator developed for CF, in patients with BE.

- WP11 supports novel outcome measures for clinical trials and analysis of EMBARC registry data. This work supports the POL7080, ALX-009 and QBW251 clinical trials. In addition it will build on the success of the registry built in WP5 by beginning to analyse the samples and data gathered.

Summary of progress versus plan since last period

This is the fifth periodic report of the iABC consortium. Year five began with the fourth General Assembly meeting which took place in Madrid on September 27th 2019. The meeting included representation from the newly proposed work packages, providing the opportunity to discuss integration and support capacity across the academic institutions. Amendment #2, which confirmed the introduction of the new programmes, was signed in September 2019 and the teams, understanding that timescales were restricted, made a rapid start on set up activities. Amendment #3 was also signed during this period to acknowledge Dr Peter Pertel joining the project as Coordinator. Throughout this period the consortium has continued to make progress against the aims of the project while managing another period of change. Work to complete the analysis of the WP4 iBEST study data escalated and the final clinical study report was issued in January 2020. The EMBARC patient registry has continued to grow and provide a valuable repository of data for clinicians and academics. The level of interest in this data world-wide remains constant as the number of papers both published and in progress confirms. To add to this body of knowledge, WP11 also developed during this period to further validate novel bronchiectasis endpoints using EMBARC biobank samples from other studies. The three clinical studies planned in WPs 8, 9 and 10 made progress throughout period 5 in terms of recruiting CROs and introducing regular trial steering committee meetings to refine protocols and begin study set up. The feature of this year, however, has been the emergence of the COVID-19 pandemic which had a considerable impact on both the ability of the studies to access clinical facilities and on the availability of clinical academics. At the time of reporting it is estimated that the studies are at least 6 months behind plan. The teams working on the Murepavadin study in WP7 and WP8 have been particularly affected as a drug reformulation was necessitated in Q1 2020 and all suppliers experienced restrictions. Recovery from COVID-19 delay is in progress, however, and the consortium continues to work well as a team towards the amended milestones and deliverables.

Significant achievements since last report

Key achievements this period include:-

- The EU Bronchiectasis registry EMBARC continues to exceed original targets, with over 19,000 patients now enrolled. Partnerships have been formed with registries in India and Australia, providing access to the data of 23,000 patients making EMBARC the largest such data resource in the world. Dissemination activities have accelerated considerably during this reporting period
- The iBEST study CTR was completed and both the study design and outcomes have been published. There has been considerable interest in the findings among the academic, clinical and pharmaceutical communities and it is anticipated that it will form the basis of future trials.
- Microbiome analysis of all iBEST samples and quantification of load has been completed.
- Automated measurements of airway-artery dimensions have been successfully obtained for all available iBEST patient scans.
- Pre-clinical toxicity testing of Polyphor's Murepavadin in rodents and non-human primates has been successfully completed and regulatory submission is underway. A CRO has been procured in preparation for a Phase I clinical study in Q4 2020
- A successful Phase I study of Alaxia's ALX-009 in healthy volunteers has been completed and the follow-up Phase I in cystic fibrosis and bronchiectasis patients is ongoing.
- ALX-009 efficacy has been further tested against a number of bacterial strains during this reporting period with considerable efficacy demonstrated on Gram negative bacteria, including some multi-resistant clinical strains.
- A CRO has been procured and regulatory submission is underway in preparation for the start of a Phase II study of Novartis' QBW251 in bronchiectasis patients

2 Summary of progress against objectives

2.1 Summary table

Work - Package	Deliverable (number and short title)	Date Due (Annex I- description of work)	Completed (Yes/Not yet/Partially)	Dissemination level	Related document attached (Yes/No/Not applicable)
4	D4.2 Phase II trial of TIP in BE patients (abbreviated report of key outcomes).	M35	Yes. The Clinical Trial Report has been completed	CO	Yes. Report has been uploaded to SOFIA
4	D4.7 Publication of iBEST1 study design	M44	Yes. The study has been published in the Journal of Pulmonary Pharmacology & Therapeutics vol 58 2019. doi.org/10.1016/j.pupt.2019.101834	PU	Yes. The publication has been added to SOFIA
4	D4.8 Publication of iBEST1 study results	M56	Yes – the study has been published in the European Respiratory Journal Vol 56 Issue 3. DOI: 10.1183/13993003.01451-2020	PU	Yes – the publication has been added to SOFIA
6	D6.4 NGS microbiome analysis of samples collected in Phase II TIP dose finding study and comparison of exploratory molecular and conventional microbiological endpoints.	M56	Partially: Primary analysis has been completed. Comparison of results with conventional microbiological results is ongoing.	PU	Yes
6	D6.9 Interim analysis (Phase II TIP dose finding study) of the responsiveness of LCI endpoint in comparison to conventional FEV1 endpoint and CT parameters.	M56	Partially: Analysis of LCI data completed. Comparison of responsiveness with CT parameters to be determined.	PU	No
6	D6.10 Interim analysis of LCI data (WP4) and comparison with other outcome measures (FEV1, quantitative culture, microbiome analysis).	M48	Partially: Analysis of LCI data completed. Comparison with other outcome measures ongoing.	PU	Yes. Paper uploaded to SOFIA
6	D6.13 Automated measurements of airway-artery dimensions for BE patients.	M42	Partially. Automated AAR analysis measures have been obtained. Resulting data will be delivered shortly.	CO	Not applicable
7	D7.10 Full report on pre-clinical development of murepavadin solution formulation as inhalation therapy, including results of inhalation toxicology	M60	Not yet. Now expected M65	CO	No

Work - Package	Deliverable (number and short title)	Date Due (Annex I-description of work)	Completed (Yes/Not yet/Partially)	Dissemination level	Related document attached (Yes/No/Not applicable)
7	D7.11 Report on development of a liposomal formulation for inhalation	M59	Not yet.Delays incurred due to change in test plan Now expected M77	CO	No
8	D8.1 Regulatory approval for Phase I study on POL7080 in healthy subjects. Submission of final trial protocol to IMI.	M56	Not yet. Regulatory submission expected M62. Approval anticipated M64.	CO	Final study protocol has been submitted with the Y5 report pack
9	D9.1a Submission of study approvals package for Phase I ALX-009	M48	Yes. The clinical trial submissions have been completed.	CO	Yes - documents have been uploaded on SOFIA
9	D9.1b Confirmation of completion of site selection for ALX-009 Phase I	M50	Yes. Site selection has been completed	CO	Yes - documents have been uploaded on SOFIA
9	D9.2 Phase I Clinical Study Report	M60	No. The clinical study was delayed due to COVID-19	CO	No
9	D9.3 Phase I Microbiome analysis report (QUB)	M60	No. The clinical study was delayed due to COVID-19	CO	No
9	D9.3b Submission of the study approvals package for Phase II ALX-009 study	M60	No. The Phase I clinical study was delayed due to COVID-19	CO	No
10	D10.1 Submission of study approvals package for Phase II QBW251 study	M49	Not yet. The submission to regulatory authorities is ongoing in UK, Germany and Spain. Completion expected by M63	CO	Final study protocol has been submitted with the Y5 report pack
10	D10.2 First Patient first visit in Phase II trial of QBW251	M59	No. The Phase II clinical study was delayed due to COVID-19. FPFV now expected M66	CO	Not applicable

Work - Package	Milestones (number and short title)	Date Due (Annex I-description of work)	Completed (Yes/Not yet/Partially)	Dissemination Level	Related document attached (Yes/No/Not applicable)
6	M6.7a Results of LCI Healthy volunteer study	M52	Yes	PU	Yes
6	M6.8 BE Scoring baseline CTs: Image analysis baseline Phase II (Bauman and Hartmann scoring, PRAGMA-BE).	M57	Hartmann, Bauman and PRAGMA-BE (BEST-CT) image analysis methods are completed. Data has been sent to Novartis and has been included in the study database	PU	Paper final draft is currently at co-authors. Submission in Q4 2020
6	M6.9 Exploratory sputum inflammatory biomarker endpoints determined	M47	Partially. Initial analysis completed. Further analysis to be undertaken when all molecular analysis completed.	PU	Yes
7	M7.10 Pre-clinical inhalation toxicology of POL7080 solution formulation completed.	M54	Yes	CO	Not applicable (Deliverable D7.10)

Work - Package	Milestones (number and short title)	Date Due (Annex I- description of work)	Completed (Yes/Not yet/Partially)	Dissemination Level	Related document attached (Yes/No/Not applicable)
7	M7.11 Development of POL7080 completed to enable decision on whether to proceed to clinical trials.	M54	Yes	CO	Not applicable (Deliverable D7.10)
7	M7.12 Development of a Liposomal Formulation for inhalation completion	M54	Partially. Delays incurred due to change in testing protocol and COVID-19 restrictions	CO	Not applicable (Deliverable D7.10)
8	M8.2 Regulatory approvals obtained for Phase I study on POL7080 in healthy subjects.	M56	Not yet – Regulatory submissions are planned September 2020	CO	No
9	M9.1 Regulatory approvals obtained for revised Phase I study design	M47	Yes	PU	Yes
9	M9.2 Last patient Last visit in Phase I study	M56	Not yet. The clinical study was delayed due to COVID-19 restrictions	CO	No
9	M9.3 Safety and tolerability determined in healthy volunteers, CF and NCFBE patients	M57	Not yet. The clinical study was delayed due to COVID-19 restrictions	CO	No
9	M9.4 Regulatory submission of phase IIa study in CF patients	M59	Not yet. The Phase I clinical study was delayed due to COVID-19 restrictions	CO	No
10	M10.1 Formation of trial steering committees	M44	Yes	CO	Yes. Minutes of Kick off meeting attached
10	M10.2 Site selection and pre-identification complete for phase II QBW251study	M55	Not yet. Site selection is ongoing with 13/15 sites engaged. Completion expected M62	CO	Yes. Site status list attached
10	M10.6 Regulatory approvals obtained	M49	Not yet. The submission to regulatory authorities is ongoing in UK, Germany and Spain. Completion expected by M62. Approval anticipated M64	CO	No
10	M10.3 First patient first visit in Phase II trial of QBW251.	M59	Not yet. FPFV is now planned for M65	CO	No
11	M11.1 WP11 kickoff meeting	M45	Yes	CO	Yes. Meeting minutes attached
11	M11.2 Transfer of registry samples from UNIVDUN to QUB	M52	Partially: Material Transfer Agreement for samples currently under review by QUB legal department.	CO	No

The following activity has also taken place where no deliverables/milestones were foreseen for this period.

Work package 1

The COVID-19 pandemic had an impact on the project plan during this period, in that many of the lab activities in both the academic and commercially contracted institutions were suspended as a result of mandatory governmental restrictions. In addition, clinicians were naturally diverted to COVID-19 patient facing priorities. Despite these restrictions, each work package made their best efforts to continue work where possible. Team meetings were maintained and focus was moved to write-up or planning activities where lab work was not possible.

The annual General Assembly meeting took place in Madrid on 27th September 2019. The assembly this year had a large participation this year as we discussed the outcomes of the terminated iBEST1 study (WP4) and introduced proposed new programmes of work.

This period began with the signature of amendment #2 to the grant agreement in September 2019. This amendment introduced a number of significant changes to the project plan. The withdrawal of the Novartis product TIP, resulted in the termination of work package 4. This provided the opportunity for a new EFPIA partner, Alaxia SAS, to join the consortium. The Phase I and potential Phase II studies of the Alaxia drug ALX-009 were added to the project plan in new work package 9. Novartis also introduced a Phase II study of QBW251 in the new work package 10. The decision was also taken to terminate the novel endpoints work package 6 which had been closely linked to work package 4 and replace it with a newly designed programme of work which covered all new clinical studies, in work package 11.

The first two quarters of this period were therefore focussed on the preparation and start-up activities related to these new programmes of work. A public procurement tender process was carried out and a contract awarded to TMC Pharma to manage the Novartis QBW251 clinical study. In parallel, amendments were signed to accommodate the existing contract between Alaxia and their contract research organisation Eurofins Optimed.

Material transfer discussions were also initiated to begin the process of moving samples from the ORBIT clinical studies from the University of Dundee to Queen's University Belfast for sequencing.

Preparations began for the Polyphor clinical study in work package 8 with a public procurement tender process. A contract was awarded to the clinical research organisation, Celerion Ltd, to manage the Phase I POL7080 (Murepavadin) study.

Dissemination activities have continued to increase during this period, albeit more slowly than anticipated due to the COVID-19 interruptions.

Work package 4

The iBEST1 clinical study was concluded in March 2019 and database lock was achieved in May 2019. Throughout period 5, considerable work among the trial steering committee, Novartis and the CRO ICON to complete and agree the final Clinical Study Report. With this report, work package 4 is operationally completed, however there has been considerable interests in the findings of this study, so dissemination of data will continue and further papers are anticipated.

Work package 5

All planned milestones and deliverables in this work package have been achieved. However, ongoing data collection and follow-up of patients continues beyond the original recruitment targets and is approaching 20,000 patients, which is double the original target.

Work package 7

During this reporting period, a significant issue was discovered during pre-clinical formulation testing.

The Murepavadin formulation used for the pre-clinical inhalation toxicology studies was based on the original iv-formulation and had a pH of 5. This formulation had considerable toxicology and stability data, gathered from the IV preclinical and clinical studies and had achieved an acceptable long-term stability. However, during the pre-clinical studies as an inhaled formulation in Q4 2019, it was discovered that at this acidic pH and, due to the presence of acetate as counter-anion of murepavadin, the solution had a bad smell, caused by significant protonation of acetate to acetic acid. It became clear that it would be prudent to develop a less acidic formulation with a pH closer to physiological levels with less acetic acidic smell/taste in order to be acceptable

to patients. Hence, after discussion with the consortium, it was decided to delay phase 1 and invest in a novel murepavadin neutral formulation through an in-house Polyphor formulation program. The new solution required specific properties including stability and the ability to be nebulized with the correct physicochemical properties. The development of this new formulation of inhaled Murepavadin has added approximately 6 months to the previously communicated timelines for WP7 and has necessitated the re-design of the protocol for the WP8 clinical study.

A large portion of the work this reporting period therefore involved reformulation of the original IV formulation that proved suboptimal for inhalation. The Polyphor team succeeded in delivering an acceptable formulation within a comparably short time. The new solution required specific properties including stability and the ability to be nebulized with the correct physicochemical properties and Polyphor have worked closely with the device manufacturer, Pari, in developing these properties. Amendment #4 to the grant agreement was submitted to reconfigure the POL7080 programme within Annex 1 and approved by IMI in August 2020.

The preparation for the Phase I clinical trial also featured heavily this period. The laboratory of Professor Antoni Torres at FCRB in Barcelona was contracted to perform PK/PD and efficacy studies in swine, to generate necessary data ahead of the clinical trial development.

Work package 8

This work package had to be re-written due to the issue with formulation discovered in WP7. The changes to the programme were approved in amendment #4 to the grant agreement. The beginning of the clinical study was, however, moved out by approximately 6 months.

During this period a public procurement tender process was undertaken to procure a CRO to manage the clinical trials. The contract was awarded to Celerion Ltd and work has since commenced to begin study start up. The Clinical Trial Application submission is planned for September 2020 with patient enrolment expected to begin before the end of 2020.

Work package 9

During this period Trial Steering Committee meetings continued. Progress of the Phase I study was monitored. The initial phases were largely completed eg Phase I study in HV, before March 2020 at which time all clinical trial activity was halted due to COVID-19 restrictions.

Work package 10

During this period Trial Steering Committee meetings were initiated and the Phase II study protocol was completed with the input of clinicians. A procurement process was carried out and TMC Pharma were contracted as the CRO for the study. Site identification took place throughout Q2 2020 and the process of site enrolment began. At the time of reporting, regulatory submissions have taken place in Spain, UK and Germany.

2.2 Description of progress for delayed milestones/deliverables not yet completed or partially completed

Work package 6

Milestone 6.8: Prototype 2.1 automated AA + AWA analysis.

The current automated AA and AWA analysis (prototype 1.1) is not yet fully automatic as it requires manually extracted airway centrelines as input. This is a tedious and time-consuming task, requiring roughly half a day per

scan. We are developing a fully automatic AA + AWA analysis (prototype 2.1) by combining i) a robust and automatic airway extraction method, and the computation of AAR measures from prototype 1.1. The airway extraction method is based on state-of-the-art deep convolutional neural networks, which have outperformed other existing algorithms in many image processing tasks. We will use the manual measurements obtained in a subset of 28 scans as a ground-truth reference to calibrate the method to segment accurately the very deformed airways with BE. We may also use the vessel segmentations already obtained by prototype 1.1 to help the method segment very difficult small airways.

The completion of this milestone will be according to the planning or shortly after. In the latter case, there will be no impact on other tasks as this is the last action for Milestone M6.8.

M6.9: Exploratory sputum inflammatory biomarker endpoints determined (TIP Phase II study)

The following inflammatory biomarkers have been analysed in sputum supernatants collected in the iBEST trial: Elastase, IL-8, IL-1b, HMGB-1 and Calprotectin. In total 606, sputum samples were tested and the final results database sent to ICON on 03 Jun 2019. Initial analysis of changes in inflammatory biomarkers with time and treatment has been undertaken. Further analysis will be undertaken when all molecular analysis completed.

D6.4: NGS microbiome analysis of samples collected in Phase II TIP dose finding study and comparison of exploratory molecular and conventional microbiological endpoints.

Six hundred and ninety-two samples collected in the iBEST trial have been processed for microbiome analysis: 621 sputum samples and 71 swab samples. All sputum samples have been sequenced and data analysed for change in relative abundance of P. aeruginosa and ecological parameters with time and treatment. P. aeruginosa load has also been determined by qPCR and compared with quantitative culture results. Next-generation sequencing microbiome analysis revealed that a number of patients were also positive for Haemophilus influenzae; therefore, we developed a qPCR assay to quantify bacterial load of this organism in sputum samples. Analysis of n=621 samples is currently ongoing. Resistome analysis using shotgun metagenomics is also ongoing with samples from patients in Cohort C of the iBEST study. Once completed, a final analysis will be undertaken to compare exploratory and conventional microbiological endpoints.

D6.9: Interim analysis (Phase II TIP dose finding study) of the responsiveness of LCI endpoint in comparison to conventional FEV1 endpoint and CT parameters.

Data from the subgroup of patients with Lung Clearance Index (LCI) data has been analysed in accordance with the study protocol (Change from baseline and shift tables in LCI at each post-baseline visit and a responder analysis) and summarised in the final Clinical Study Report from Novartis.

Data on LCI data quality control and feasibility of LCI as an outcome measure in bronchiectasis clinical trials has also been included in the final study report and published in an original article:

Multiple Breath Washout (MBW) in bronchiectasis clinical trials – Is it feasible? O'Neill, K., Ferguson, K., Cosgrove, D., Tunney, M., De Soyza, A., Carroll, M., Chalmers, J. D., Gatheral, T., Hill, AT., Hurst, JR., Johnson, C., Johnson, C., Loebinger, M. R., Angyalosi, G., Haworth, C. S., Jensen, R., Saunders, C., Short, C., Davies, J. C., Elborn, S. & 1 others, 19 Jul 2020, (Accepted) In : ERJ Open.

Once all CT data is available, further analysis of LCI data will include exploring the (i) change from baseline in LCI compared with FEV % predicted and (ii) the association between LCI and CT parameters.

D6.10: Interim analysis of LCI data (WP4) and comparison with other outcome measures (FEV1, quantitative culture, microbiome analysis)

As described above, data from the subgroup of patients with LCI data has been analysed in accordance with the study protocol. Comparison with other outcome measures such as quantitative culture and microbiome analysis is ongoing and will be finalised once all exploratory data available.

D6.13: Automated measurements of airway-artery dimensions for BE patients.

Automated airway and vessel segmentations and AAR analysis measures have been successfully obtained for scans of 84 BE patients. The segmentations have been calibrated by comparing the measures i) airway diameter and ii) AAR ratio, with manual measurements obtained on a subset of 28 scans. The AA-method parameters were optimised through this calibration to give the best correlation between the automated and manual measurements. Through visual inspection of a subset of measures, airway lumen diameter and airway tapering were found to be a relevant measure to mark the presence of BE. A BE biomarker based on airway tapering measures is being investigated, and will be compared with Bauman and Hartmann scoring, and PRAGMA-BE, in a journal paper being currently written.

Work package 7

As described in section 2.1, the discovery of an issue with the formulation resulted in approximately 6 months delay. As a result milestones M7.10, M7.11, M7.12 and deliverables D7.10 and D7.11 have been impacted. Work has continued and been expedited where possible and partners Pari and Baccinex were particularly helpful in providing slots for their necessary tasks within this program. However, national COVID-19 restrictions and re-prioritisations due to the pandemic have impacted both Polyphor and the subcontractor suppliers carrying out the work. Polyphor are working with their suppliers to complete the final reports and at this stage it is estimated that the outstanding milestones and deliverables will be completed by the end of 2020.

Work package 8

As described in section 2.1, the discovery of an issue with the formulation and the need to re-formulate resulted in approximately 6 months delay. This has impacted milestone M8.2 and deliverable D8.1. Work has continued with the CRO, Celerion, throughout the COVID-19 restriction period, however, and it is now anticipated that CTA submission will take place at the end of September 2020 (M62) with approval expected by M64. The version of the protocol which will be submitted for regulatory approval has been included as part of this Y5 report pack for IMI records.

Work Package 9

Due to the COVID-19 restrictions, all clinical site opening planned in April 2020, including at Hospices Civils de Lyon (HCL) where the study had been ongoing, was placed on hold. The ALX-009 clinical program is expected to restart in September 2020 in France and later on in UK if the health situation allows it. Thus, Milestones M9.2, M9.3 planned for M56 and M57 and Deliverables D9.2, D9.3 planned for D60 are not realized.

For completing Clinical trial Phase I, we'll have a delay. Milestones M9.2, M9.3 and Deliverables D9.2, D9.3 will be delayed by 6 to 12 months (6months is a minimum), 12 months delay seems for us more realistic taking into account anticipated patient recruitment difficulties due to the ongoing pandemic.

Work package 10

Due to COVID-19 restrictions, start-up activities for the QBW251 Phase II study were delayed in Q2 2020. Deliverable D1.0 is now expected in M62 with FPFV now expected in M64

Work package 11

M11.2: Transfer of registry samples from UNIVDUN to QUB

Review of the Material Transfer Agreement for samples is currently ongoing by QUB legal department. Once completed, samples will be transferred from Dundee to QUB.

2.3 Deviations from Description of Work

Work Package 5

There have been no major deviations from the description of work which impact on delivery or the budget. The major deviation is the increase in recruitment numbers, which has been achieved with co-funding and appropriate use of the existing funding. Expansion of the registry and inclusion of bio-banking and additional dissemination activities have been achieved within the existing description of work/budget.

Work Package 7

All deviations to the activities described in DoW V3.5 October 2019v2 have recently been captured in amendment#4 to the grant agreement. This amendment introduces DoW V4.0 June 2020 Revised which reflects the current work plan. Work package 7 has been updated to include increased pre-clinical testing of a new formulation of Murepavadin, including the addition of swine testing to determine PK/PD ahead of the clinical trial – this will be carried out at FCRB who have re-joined the iABC consortium specifically for this purpose.

Work Package 8

All deviations to the activities described in DoW V3.5 October 2019v2 have recently been captured in amendment#4 to the grant agreement. This amendment introduces DoW V4.0 June 2020 Revised which reflects the current work plan. The clinical study has been redesigned to include a Phase I extension with an MAD arm in healthy volunteers and the development of a formulation device to be used in Phase II. Phase II will now fall outside the iABC project and will be funded separately by Polyphor. The revised Phase I study contains 3 parts as depicted in Figure 1 below

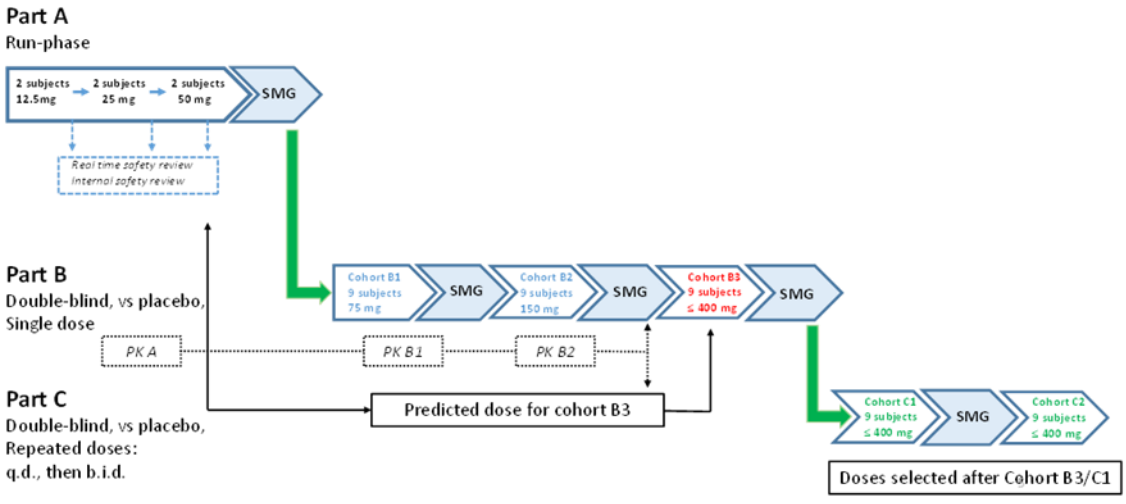


Figure 1: Revised POL7080 Phase I study design

3 Summary of Major Achievements and key dissemination activities

3.1 Major achievements

This report reflects another period of great change within the iABC consortium and its programme of work. Despite this period of change and the impact of the global COVID-19 pandemic, the consortium are pleased to report that valuable progress continued to be made. The following are the highlights of the period.

Work package 4

The iBEST study CTR was completed and both the study design and outcomes have been published. There has been considerable interest in the findings among the academic, clinical and pharmaceutical communities and it is anticipated that it will form the basis of future trials.

Work package 5

WP5 has established a highly successful pan-European registry that is now regarded as a model for internationally collaborative research in rare lung diseases. The EMBARC team support the enrolling sites, provide technical support of the EMBARC websites and case report forms, resolve data queries and provide quality control of the EMBARC data. EMBARC has achieved an aligned set of data fields agreed between EMBARC, the US COPD foundation and the Lung Foundation of Australia. All of the European collaborators of EMBARC have agreed to utilise the same electronic case report form and this has been successfully deployed to our stakeholders.

The EMBARC website is available at www.bronchiectasis.eu and serves as a focal point for data entry and also for updates on bronchiectasis activities generally, and particularly within ERS and related iABC.

Our initial projects proposed recruitment of 1000 patients by April 2016, and 4000 patients by the end of 2017. This rate of recruitment was estimated in order to achieve enrolment of 10,000 patients by the end of 5 years.

At the time of writing we are far ahead of the target recruitment rate, with more than 19000 patients enrolled into the study from 30 countries. Including our partner registries in India and Australia we have more than 23,000 patients data available for analysis including detailed longitudinal data. This far exceeds the original estimates and makes the EMBARC registry the largest such data resource in the world. The registry is now primarily focussing on long term data collection rather than the enrolment of new patients because the incremental value of new cross-sectional data is low, whereas longitudinal data is of high value to our researchers.

Initial analysis of the data shows that the data are representative, with demographics, treatment patterns and severity characteristics which are in keeping with what is already known about bronchiectasis in Europe.

Dissemination activities have greatly accelerated in the past 18 months and EMBARC data is now being used and published widely including in peer reviewed journals.

The EMBARC registry is now sustainable beyond the iABC funding having received euro1m from the European Respiratory Society this year to expand recruitment beyond the 10,000 patients that were originally funded by iABC. This represents the final milestone that we had been set.

Work package 6

Automated measurements of airway-artery dimensions for BE patients: Airway and vessel segmentations, dimension measures, and luminal and outer wall AAR and tapering measures have been successfully obtained

for all available iBEST scans, except for one case which was excluded due to severe motion artefacts. This was achieved by calibrating the AA-method using the manual measurements of a subset of 28 scans.

Microbiome analysis of all iBEST samples and quantification of load by qPCR have been completed.

Work Package 7

This reporting period saw the finalization of the preparations needed to proceed to clinical studies with murepavadin, a major milestone. The preclinical toxicity in rodents and non-human primates was successfully concluded and the documentation required for regulatory submissions was established.

In more detail, a neutral formulation (pH 7) has been developed by Polyphor, based on mixing two solutions just before inhalation to avoid the bad smell of acetic acid. The solution had to undergo stability tests at a qualified third party (Polyphor's long-term partners for this activity are Interlabor and Baccinex). The device manufacturer, Pari, has confirmed the proper device head and mesh selection for the new formulation. The currently developed formulation will be used in the Phase 1 study.

In addition, a commercial two-chamber device is under consideration for the Phase 2 to provide a patient-friendly and simple to use formulated murepavadin. In order to make a user-friendly device, the Polyphor CMC team is developing a formulation that can be used in a two-chamber device, which is planned for the Phase 2 study. This improves shelf-life and patient-friendliness, a necessity for the Phase 2 studies.

In addition to the originally planned studies, swine studies were successfully completed in order to assess PK/PD in preparation for the clinical study. These results helped determining the correct starting dose used in the clinical phase 1 study.

Regulatory advice was sought to understand if additional pre-clinical toxicology studies would be required on the new formulation to gain CTA approval.

The collaboration with Polymun is very fruitful and so far, two initial formulations have been successfully designed as planned and will further be tested for stability. Having established the feasibility of producing murepavadin liposome, the next steps will be the characterization of two liposomal formulations for stability, efficacy in vitro and in vivo and PK/PD. Further development options are in discussion. The development of the liposomal formulation is successful but is delayed due to COVID19-related issues for manufacturing the two formulation feasibility batches.

A number of publications and presentations at scientific/medical conferences were published, prepared, and/or held (see table in section 2.2). A major need for the reclassification of several micro-organisms chronically infecting persons with cystic fibrosis and bronchiectasis has become apparent, in particular Pandoraea and Ralstonia species. Accurate differentiation of species may support treatment decisions for these potential pathogens.

Moreover, two publications on the activity of murepavadin on biofilms and antibiotic resistance development have been prepared and sent for review to the different microbiology partners of the iABC consortium.

Work package 8

The clinical science team, together with the Trial Steering Committee and clinical advisors established the clinical trial study plan and the detailed design of the Phase 1 study. Celerion was procured to perform the phase 1 study.

The CTA was prepared and is ready to be handed in in September 2020.

It is planned that the first patient is dosed before Year End.

The collaboration with Celerion, which was selected by QUB via a Tender Offer, was established, as was the Polyphor team managing the clinical trial.

Work package 9

During this period, Clinical study part III and IVa have been completed and we started part IVb, administration on CF/BE patients as illustrated in Figure 2

We can therefore consider ALX-009 clinical study Phase I in healthy volunteers as a major achievement of the period.

The second accomplishment during the period is the availability of EOLEASE machine. This machine has been designed to produce extemporaneously ALX-009. 2 machines have been delivered to Lyon clinical site, 1 to QUB for microbiological research (WP 11) and 6 of them are ready to leave our facilities for installation on clinical sites (Belfast, Southampton, Grenoble). The site initiation visit of the Lyon site was done and the site is ready to enrol patients in September.

Finally, the Alaxia team continued to test the efficacy of ALX-009 against a number of bacterial strains during this period. As is shown in Table 1 below, ALX-009 demonstrates 100% efficacy on Gram negative bacteria, including the multi-resistant clinical strains tested for which there are no treatment options today.

Some strains of *Pseudomonas aeruginosa* MDR, *Stenotrophomonas maltophilia*, *Pandorea* spp and *Ralstonia* spp were kindly supplied by iABC partner, Miquel Ekkelenkamp, UMC Utrecht.

Figure 2: ALX-009 Phase I study status

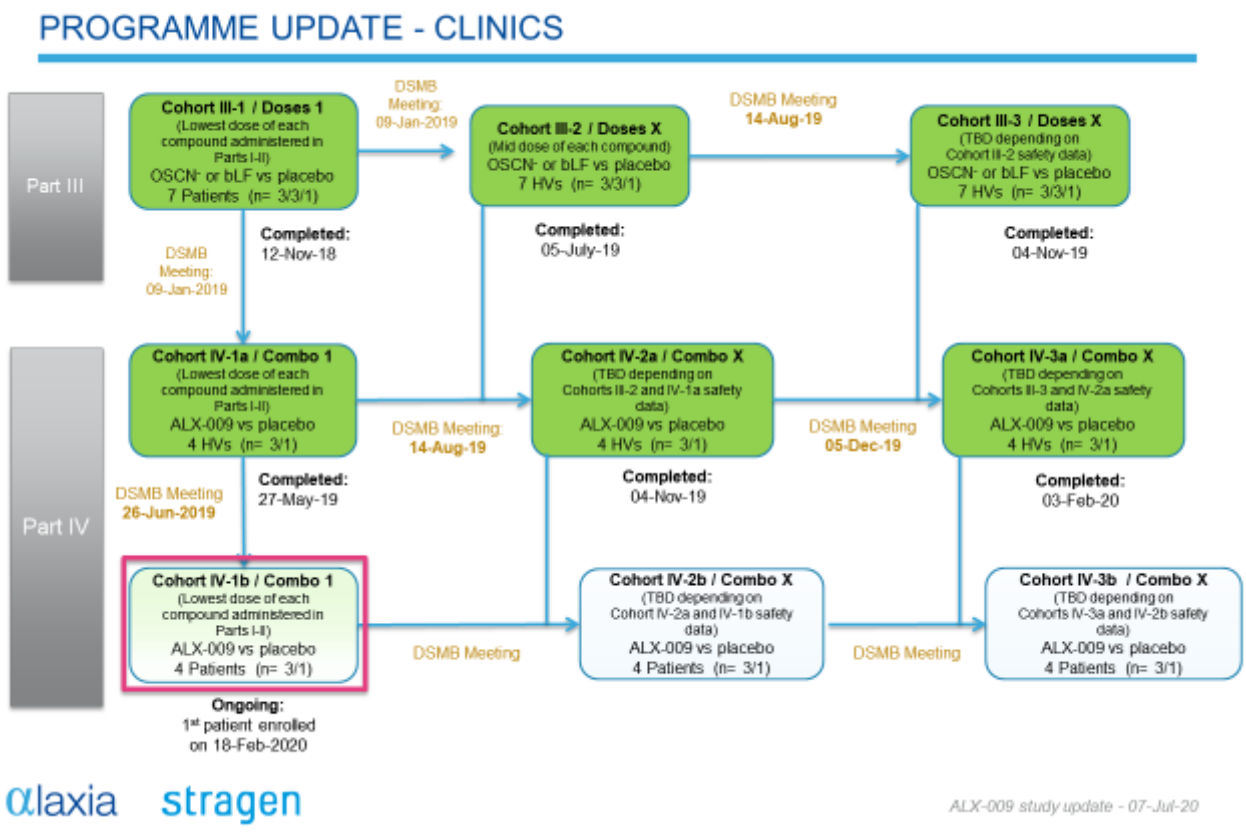
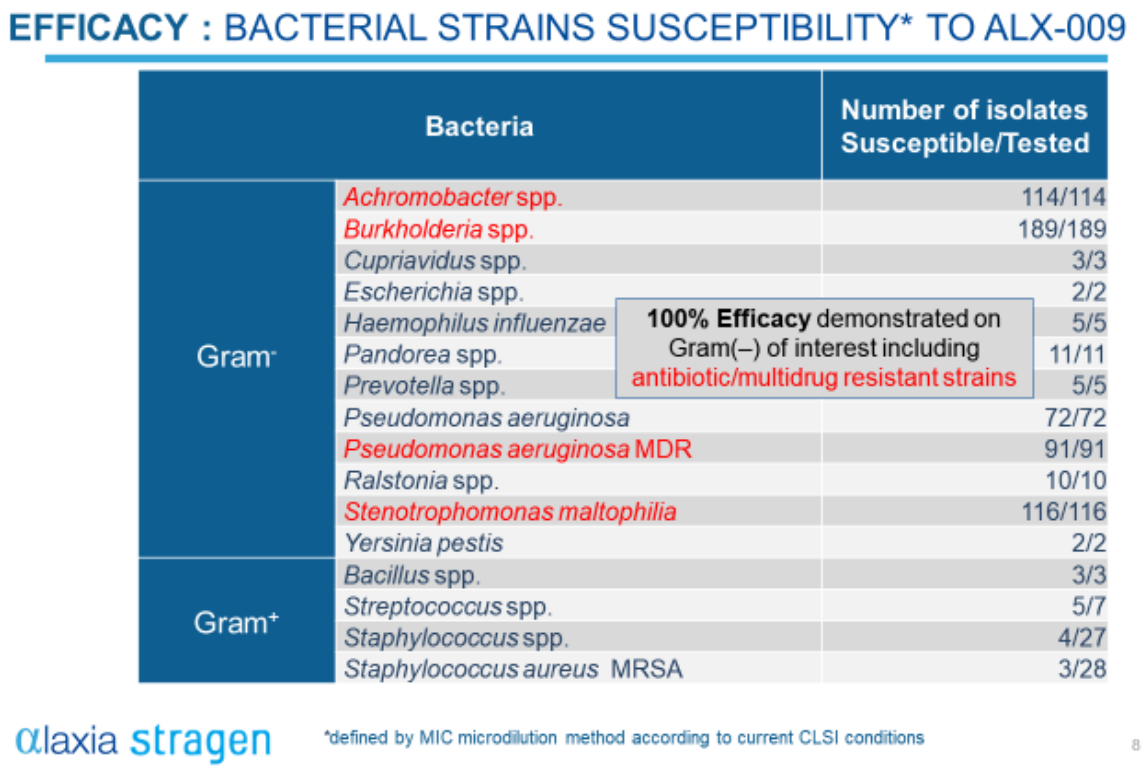


Table 1: ALX-009 Efficacy against bacterial strains tested



Work Package 10

The Trial Steering Committee reviewed and agreed the Phase II study protocol. A CRO, TMC Pharma was recruited via a public procurement process and a good working relationship has been established. Site selection is at an advanced stage and the CTAs have been prepared for submission in September 2020

It is planned that the first patient visit will take place at the end of November 2020.

3.2 Key dissemination activities

Nature of Communication	Title	Responsible Participant (and presenter when relevant)	Date/location when relevant.	Target audience
Project website	www.bronchiectasis.eu	WP5 UNIVDU	Ongoing	Public and Heathcare Professionals
Project newsletters	https://www.bronchiectasis.eu/Contents/Item/Display/4138	WP5 UNIVDUN	Quarterly	Public and Healthcare Professionals
Publication	Inhaled aztreonam improves symptoms of cough and sputum production in patients with bronchiectasis: a *post hoc* analysis of the AIR-BX studies	WP5 UNIVDUN	European Respiratory Journal Vol 56 Issue 3	Healthcare Professionals
Publication	A systematic review of pharmacotherapeutic clinical trial endpoints for bronchiectasis in adults	WP5 UNIVDUN	European Respiratory Review Vol 28 Issue 151	Healthcare Professionals
Abstract	Airway clearance techniques in patients with bronchiectasis. Data from the EMBARC Registry. A. Spinou (London, United Kingdom)	WP5 UNIVDUN	ERS congress 2020	Healthcare Professionals
Abstract	Immunodeficiency associated bronchiectasis in the European Bronchiectasis Registry (EMBARC) P. Mitchelmore (Exeter (Devon), United Kingdom)	WP5 UNIVDUN	ERS congress 2020	Healthcare Professionals
Abstract	Asthma as a co-morbidity and cause of bronchiectasis: data from the European Bronchiectasis Registry (EMBARC). E. Polverino (Barcelona, Spain)	WP5 UNIVDUN	ERS congress 2020	Healthcare Professionals
Abstract	Inhaled antibiotics improve symptoms of cough and sputum in patients with bronchiectasis: a post-hoc analysis of the AIR-BX studies M. Crichton (Dundee (Angus)	WP5 UNIVDUN	ERS congress 2020	Healthcare Professionals

`	Title	Responsible Participant (and presenter when relevant)	Date/location when relevant.	Target audience
Conference Presentation	A joint 3D UNet-Graph Neural Network-based method for Airway Segmentation from chest CTs	Antonio Garcia-Uceda Juarez	MICCAI 2019 Shenzen China	International audience of medical imaging researchers
Presentation	A joint 3D UNet-Graph Neural Network-based method for Airway Segmentation from chest CTs	Antonio Garcia-Uceda Juarez	DLMEDIA 07 January 2020	Members of the DLMEDIA (deep learning in medical image analysis) consortium
Paper	Multiple Breath Washout (MBW) in bronchiectasis clinical trials - is it feasible?	Katherine O'Neill	European Respiratory Journal accepted July 2020	Scientific community
Presentation	Presentation of iBEST study microbiome analysis	Gisli Einarsson	London. British Thoracic Society Winter meeting Dec 2019	Scientific community
Publication	Whole-genome analysis of Pandoraea species strains from cystic fibrosis patients.	UMCU, SERMAS-HURYC, QUB,	Future Microbiology Vol 14, No.16 November 2019	Clinical microbiologists
Publication	Susceptibility of Pseudomonas aeruginosa Recovered from Cystic Fibrosis Patients to Murepavadin and 13 Comparator Antibiotics	UMCU, SERMAS-HURYC, QUB, POL	Antimicrobial Agents and Chemotherapy November 2019	Clinical microbiologists, Pulmonologists, ID-specialists
Publication	Draft genome sequence of the strain 16-537536, isolated from a patient with bronchiectasis and its relationship to the Pseudomonas koreensis group of the Pseudomonas fluorescens complex	UMCU, SERMAS-HURYC	BMC Research Notes Vol 13 2020	Clinical microbiologists
Publication	Draft genome sequence of a Haemophilus parainfluenzae strain isolated from a patient with chronic obstructive pulmonary disease	UMCU, QUB	ASM Microbiology Resource Announcement. March 2020	Clinical microbiologists
Press Release	Alaxia joins EU consortium to combat drug-resistant lung infections Partnership in iABC project will accelerate Alaxia's development of promising antimicrobial therapy for cystic fibrosis	Alaxia	October 2019	Professional and general public
Alaxia Website update	https://www.alaxia-pharma.eu/news/	Alaxia	Ongoing	Professional and general public
Publication	Bronchiectasis in India: results from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) and Respiratory Research Network of India Registry	WP5, UNIVDUN	October 2019	Professional and general public

3.3 Use and dissemination of foreground

- The EMBARC registry is data is publically available for use and is being used by both members of the bronchiectasis research community and healthcare professionals. Details of data access is found here - https://www.bronchiectasis.eu/dataaccess. To date the registry has provided data to more than 50 unique users including 7 commercial organisations, multiple research groups as well as members of the iABC consortium.
- The foreground generated in WP7 is being published in scientific journals and/or used for the clinical development of murepavadin. Based on results from the preclinical toxicology, in-vivo models and in-vitro susceptibility testing development of the drug has advanced close to clinical phase I.
- Discussions are ongoing regarding the sharing of data gathered in WP4 through the iBEST study both internal and external to the consortium.

3.4 Overall management of the project

The management of the project continued in the same vein as period 4 with strong collaboration among the consortium. The year began with the approval of amendment #4 to the grant agreement and the implementation of considerable changes to the Description of Work. All partners continued to work together to react to these changes in the shortest time possible.

Throughout the year, the Coordination Unit continued to meet twice each month and the Management Board once per month. Each of the work packages continued their meetings as appropriate and attendance and enthusiasm in all forums remains high. It is worth noting that the forums maintained their meeting schedules as far as possible throughout the COVID-19 restrictions and this has helped smooth the resumption of activities in Q2 and Q3 of 2020 working towards three clinical studies in late Q4.

The team had initially planned to convene at the World Bronchiectasis meeting in Barcelona in June 2020, but travel restrictions meant that this was not possible. Plans are being developed to hold a virtual General Assembly at the end of October 2020 instead.

The iABC project continues to be represented at the ND4BB meetings and the interaction with other members of this group in conjunction with EFPIA has proven invaluable in terms of information exchange. Connections with EMBARC, ERS and ECFS also remain strong.

The team has also begun to look beyond the iABC project to see how we can build upon the valuable outputs from this grant. The group is largely interested in staying together as a partnership and connections have been made with other EFPIA partners who have also expressed interest in joining. Discussions will continue and plans firm up over the next reporting period.

3.5 Follow-up of recommendations and comments from previous review(s) (if applicable)

All comments and recommendations highlighted in the P4 report have been noted by the consortium and addressed where necessary.

3.6 Project plan for the remaining reporting periods

Period 6 will follow the project plan outlined in Description of Work v4.0 June 2020_revised

Work Package 1

The focus will be on implementing the new Description of Work. As remaining time is limited and the impact of the COVID-19 restrictions has been felt in most work packages, it is envisaged that the consortium will request a further no-cost extension to the project timeline to allow time to complete the three individual drug trials planned for period 6

Work Package 5

The focus continues to be on rapid dissemination of the extensive data that is available from the registry. Recruitment continues although the management board agrees that there is unlikely to be substantial additional scientific value to recruiting more patients at baseline when data is already available on nearly 20000 therefore the focus is on achieving sustained follow-up data for the patients and getting the data analysed and disseminated in peer reviewed publications. Data is being used for interactions with regulators and to support the development of clinical trials.

Work Package 6

- Completion of microbiome and resistome analysis (qPCR, shotgun metagenomics) of samples collected in iBEST-1 study and comparison of exploratory molecular and conventional microbiological endpoints.
- Analysis of data from the iBEST-1 study to determine the responsiveness of LCI as an endpoint in comparison to conventional FEV1 CT parameters and microbiological endpoints.
- Analysis of sputum inflammatory biomarker data collected in iBEST-1 study and comparison with conventional and other exploratory endpoints.
- A journal paper is being written reporting the Bauman and Hartmann scoring, and PRAGMA-BE, together with the automated AAR analysis measures, of iBEST scans.
    - A journal paper is being written reporting a robust method to automatically extract airways from CT scans based on state-of-the-art image processing methods.
    - The software for automated AA + AWA analysis will be further developed by combining a robust automatic airway extraction method with the computation of AAR measures from prototype 1.1. This will facilitate AA+AWA analysis in future studies.
- Publication of results in peer-reviewed journals

Work Package 7

- The animal model of CF will be developed further.
- The biofilm model has been developed and further studies are on-going.
- Analysis of the Whole Genome Sequencing data will be continued.
- A report will be generated on the tentative ECOFFs and feasibility of separate breakpoints for inhaled antibiotics.

- CMC – final preparation, including production for the clinical study phase 1 in health volunteers.
- Development of a two-chamber device in preparation for the clinical study phase 2 in CF patients.
- Swine studies (infected and non-infected pig model) are being planned in collaboration with Prof Torres.
- The completion of the development of the liposomal formulation is delayed to M71.

Work Package 8

The revised design of the clinical study phase 1 was completed and all necessary preparations have been completed or nearly completed during the reporting period in order to file the CTA with the goal to dose the first patient before Year End.

The remaining tasks for the remaining reporting periods are:

- Final preparation of the clinical trial phase 1
- Finalize and file CTA document
- Production of drug product
- Shipping drug product to the clinical trial site
- Running and completing clinical study phase 1

Work Package 9

Phase I part IVb clinical trials will be carried out and preparation will begin for Phase II study with ALX-009

Work Package 10

Phase II QBW251 study will begin Q1 2020

Work Package 11

This work package will support the ALX-009, POL7080 and QBW251 clinical studies. In addition, EMBARC registry material will be transferred from UNIVDUN to QUB to begin testing

The following deliverables and milestones are planned

Work - Package	Deliverable (number and short title)	Deliverable name	Nature	Planned delivery date
6	D6.4	NGS microbiome analysis of samples collected in Phase II TIP dose finding study and comparison of exploratory molecular and conventional microbiological endpoints.	R	M63
6	D6.9	Interim analysis (Phase II TIP dose finding study) of the responsiveness of LCI endpoint in comparison to conventional FEV1 endpoint and CT parameters	R	M63

Work - Package	Deliverable (number and short title)	Deliverable name	Nature	Planned delivery date
6	D6.10	(WP4) and comparison with other outcome measures	R	M63
6	D6.13	Automated measurements of airway-artery dimensions for BE patients	R	M65
7	D7.4	Murepavadin biofilm testing results, including results BioFlux development.	R	M77
7	D7.5	Inhaled murepavadin efficacy results of in vivo testing in acute infection models	R	M70
7	D7.6	Report on the effects of murepavadin enteral administration on lung flora and gastro-intestinal flora.	R	M70
7	D7.7	Report on the development of the βENaC-Tg mouse model of chronic pulmonary infection and the use of this model for efficacy testing.	R	M77
7	D7.8	Report on WGS analysis.	R	M77
7	D7.9	Report on the development of breakpoints for P. aeruginosa in CF and for inhalation therapy.	R	M77
7	D7.10	Full report on pre-clinical development of POL7080 solution formulation as inhalation therapy, including results of inhalation toxicology.	R	M65
7	D7.11	Report on development of a liposomal formulation for inhalation	R	M77
7	D7.12	Decision of moving forward into clinical development.	O	M65
7	D7.13	Report on swine studies PK/PD and efficacy.	R	M77
7	D7.14	Report on development of two-chamber formulation and device.	R	M77

Work - Package	Deliverable (number and short title)	Deliverable name	Nature	Planned delivery date
8	D8.1	Regulatory approval for Phase I study on POL7080 in healthy subjects. Submission of final trial protocol to IMI.	R	M64
8	D8.2	Successful Phase I study determining the maximal tolerable dose of POL7080 in healthy subjects and demonstrating its safety (abbreviated report of key outcomes).	R	M77
8	D8.5	Data on new clinically relevant endpoints in HV such as microbiome analysis	R	M77
9	D9.2	Phase I Clinical Study Report	R	M70
9	D9.3	Phase I Microbiome analysis report (QUB)	R	M70
9	D9.3b	Submission of the study approvals package for Phase II ALX-009 study	R	M75
9	D9.4	Phase IIa Clinical Study Report	R	M77
9	D9.5	Phase IIa Microbiome analysis report (QUB)	R	M77
9	D9.6	Publication of study results	R	M77
10	D10.1	Submission of study approvals package for Phase II ALX-009	R	M62
10	D10.2	First Patient first visit in Phase II trial of QBW251	R	M65
10	D10.3	Phase II trial of QBW251 in BE patients (abbreviated report of key outcomes).	R	M77
10	D10.4	Publication of study results	R	M77
11	D11.1	Quantitative sputum microbiology in clinical trials	R	M77

Work - Package	Deliverable (number and short title)	Deliverable name	Nature	Planned delivery date
11	D11.2	Biorespository of clinical CF and BE respiratory isolates, linked to a database including microbial and patient information, for future research use	O	M77
11	D11.3	Biobank of blood (BE) and sputum (CF & BE) samples, linked to a database including microbial and patient information, for future research use	O	M77
11	D11.4	NGS microbiome analysis of samples collected in clinical studies (WP8, WP9, WP10) and comparison of exploratory molecular and conventional microbiological endpoints	R	M77
11	D11.5	Analysis of sputum inflammatory biomarker data collected in clinical studies (WP8, WP9, WP10) and comparison with conventional and other exploratory endpoints	R	M77
11	D11.6	Final Analysis of CT outcome measures: Cross sectional and longitudinal comparison of CT related outcome measures to spirometry and LCI outcome measures	R	M77
11	D11.7	PRAGMA-BE) analysis of volumetric chest CTs of BE patients	R	M77
11	D11.8	Microbiome analysis of EMBARC registry samples	R	M65

3.7 Risk assessment, when appropriate

Please fill-in the table outlining key risks identified for the upcoming reporting periods and related mitigation plan. Please take into account in your risk assessment the continued relevance of the objectives and breakthrough potential. VH = Very High, H = High, M = Medium, L = Low

The consortium would like to highlight that in addition to the threats listed below, the remaining project duration is a risk to the achievement of the project objectives. It is anticipated, therefore, that a further project amendment request will be lodged in the coming period (PR6) to request an extension of the timelines to allow full completion.

Project Risk / Issue	Probability VH/H/M/L	Impact VH/H/M/L	Mitigation plan	Responsible Participant	Action to be taken	Due Date
WP1 Further changes in the consortium membership/programme of work	L	VH	Close collaboration and communication among partners. Early discussions with IMI	All	Situation to be monitored	Ongoing
WP1 The impact of Brexit	H	H	Mitigation plans to be drawn up as soon as situation becomes clear	QUB	Situation to be monitored	Nov-20
WP5 Slowness in disseminating outputs because of the scale of the registry and number of papers	H	H	Funds previously identified for other activities are being diverted into statistician time to enable more rapid dissemination	UNIVDUN	Already taken	Aug-20
WP8, WP9, WP10 CTAs not accepted and/or revisions are asked for	M	M	Answer questions quickly and adapt CTA	Polyphor, Novartis, Alaxia	Situation to be monitored	Q4 2020
WP8, WP9, WP10 COVID-19 pandemic related delays in clinical trials	M	H	Delay until enrolment and treatment of healthy volunteers is possible/ allowed again	Trial steering committees and CROs	Situation to be monitored	Ongoing

4 Finance – Cost

4.1 Cost summary

Reporting of costs incurred by IMI beneficiaries and third parties

Due to sizing the financial report has been moved to a separate file

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