Periodic Project Report

Inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis

iABC

Dr Peter Pertel
Novartis Pharma AG
Lichtstrasse 35
4056 Basel
Switzerland

Period 08/2020 – 12/2021
Reporting Period 6
Description of work - DoW v4.0 June 2020 and v5.0 July 2021 (signed Nov 2021)

Date of submission: 31 March 2022

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: ...../ ...../ .....

Signature of the Coordinator: Pertel Peter Digitally signed by Pertel Peter DN: dc=com, dc=novartis, ou=people, ou=PH, serialNumber=1141877, cn=Pertel Peter Date: 2022.03.28 15:51:05 -04'00' .....

[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:

- To determine the initial therapeutic efficacy of TIP in BE patients
- To explore novel endpoints (microbiome, LCI and CT imaging) for clinical trials in both CF and BE
- To build repositories of clinical respiratory isolates and sputum biobanks for use in future research
- To 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
- To develop an inhaled formulation and dispersion device for POL7080, a novel antibiotic with activity against *Pseudomonas aeruginosa.*
- To determine the pharmacokinetics and safety of POL7080 in HV patients.
- To evaluate the safety and tolerability of the OSCN- and LF compounds of ALX-009, separately and combined at different doses.
- To 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.
- To 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 sixth periodic report of the iABC consortium. Year six began with our annual General Assembly meeting which had to move to a virtual meeting due to COVID-19 travel restrictions. The meeting included representation from all work packages, provided an opportunity for all teams to meet and discuss progress and the effects of the pandemic on their institutions. Amendment #4 and amendment #5 were signed within this period. Amendment #4 confirmed the re-admission of Fundacio Clinic per a la Recerca Biomedica to the consortium and a change the work programme proposed by Polyphor AG. Amendment #5 again updated the Description of Work to take account of delays incurred due to the global pandemic which affected the availability of both clinicians and facilities. Despite the difficulties caused by COVID-19, the work packages continued to make progress against the aims of the project albeit slower than we would have intended. 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, EMBARC biobank samples were transferred from UNIVDUN to QUB for analysis under WP11. The three clinical studies planned in WPs 8, 9 and 10 were successful in gaining regulatory approval in period 6. The Polyphor sponsored Murepavadin study in WP8 has recruited healthy volunteers to its Phase I study and the first cohort have been treated. The Alaxia sponsored ALX-009 study in WP9 completed its Phase I in healthy volunteers and moved into the first cohort of cystic fibrosis patients. The Novartis sponsored, QBW251 Phase II study in bronchiectasis in WP10 has also begun randomising patients. COVID-19 continued to have an effect on the speed of progress however, most felt in the willingness of patients to attend clinics and take part in clinical studies and in periodic closures of clinics due to outbreaks. At the time of reporting 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
- Regulatory approval was received from the UK's Medicines & Healthcare products Regulatory Agency (MHRA) for the Murepavadin Phase I study in healthy subjects and the first doses have been successfully administered
- Alaxia completed the study of ALX-009 in healthy volunteers and received regulatory approval in both UK and France to begin the Phase I study in cystic fibrosis patients. The first patient was randomised
- The Phase II study of Novartis' QBW251 in bronchiectasis patients gained regulatory approval in UK, Germany and Spain. 13 clinical sites have been opened and 10 patients have been randomised.
- Ethical approval was received to test EMBARC samples from prior studies to add to the knowledge gained in WP11. Samples were transferred from the University of Dundee to Queen's University Belfast and testing has begun
- To further add to the knowledge gain in WP11, EMC have analysed 500 CT scans from the EMBARC registry

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)
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. As the LCI study has been discontinued, the remainder of the deliverable may be incorporated into WP11	PU	No
7	D7.4 Murepavadin biofilm testing results, including results of BioFlux development	M90	Yes	PU	Yes. Papers have been added to SOFIA
7	D7.5 Inhaled murepavadin efficacy results of in vivo testing in acute infection models	M66	Yes	PU	Yes. Reports have been added to SOFIA
7	D7.10 Full report on pre-clinical development of murepavadin solution formulation as inhalation therapy, including results of inhalation toxicology	M65	Yes	PU	Yes. Report has been added to SOFIA
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 M89	CO	No
7	D7.12 Decision to move forward into clinical development	M59	Yes	PU	Yes. Documents added to SOFIA
8	D8.1 Regulatory approval for Phase I study on POL7080 in healthy subjects. Submission of final trial protocol to IMI.	M74	Yes.	PU	Yes. Documents added to SOFIA
9	D9.2 Phase I Clinical Study Report	M60	Partially.Initial study results are available	CO	Yes. Initial study results are appended to the report
9	D9.3 Phase I Microbiome analysis report (QUB)	M60	No. The study has been terminated by Alaxia. An amendment to the Description of Work is in progress	CO	No
9	D9.3b Submission of the study approvals package for Phase II ALX-009 study	M60	No. The study has been terminated by Alaxia. An amendment to the Description of Work is in progress	CO	No
10	D10.1 Submission of study approvals package for Phase II QBW251 study	M49	Yes. Submission has been made to the authorities in UK, Germany and Spain. Approval has been given in all regions	PU	Yes. Protocol and documents have been added to SOFIA
10	D10.2 First Patient first visit in Phase II trial of QBW251	M69	Yes The first patient first visit took place in M69	PU	Yes. Letter of confirmation from TMC Pharma acting as CRO for this study has been added to SOFIA

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	M6.8 BE Scoring baseline CTs: Image analysis baseline Phase II (Bauman and Hartmann scoring, PRAGMA-BE).	M57	Yes. 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. Paper has been submitted for publication	PU	Yes. Completed paper attached
7	M7.12 Development of a Liposomal Formulation for inhalation completion	M54	Not yet. Delays incurred due to change in testing protocol and COVID-19 restrictions	CO	No
7	M7.4 Murepavadin biofilm testing results, including results BioFlux development.	M66	Yes	PU	Yes. Papers below published & have been added to SOFIA: Journal of Antimicrobial Chemotherapy, Volume 76, Issue 4, April 2021, Pages 984–992, https://doi.org/10.1093/jac/dkaa529 Published: 24 December 2020 Journal of Antimicrobial Chemotherapy, Volume 76, Issue 10, October 2021, Pages 2578–2585, https://doi.org/10.1093/jac/dkab222
7	M7.5 Inhaled murepavadin efficacy results of in vivo testing in acute infection models	M66	Yes	CO	Yes. Report added to SOFIA
8	M8.2 Regulatory approvals obtained for Phase I study on POL7080 in healthy subjects.	M56	Yes – Regulatory submission has been completed and approval received in UK	CO	Yes. Documents have been added t SOFIA under D8.1. Letter from MHRA attached
8	M8.3 First patient first visit in Phase I study of POL7080 in HV	M74	Yes – First patient first visit has been completed	CO	Yes. Letter of confirmation from Celerion acting as CRO for this study
9	M9.2 Last patient Last visit in Phase I study	M56	No. The study has been terminated by Alaxia. An amendment to the Description of Work is in progress	CO	No
9	M9.3 Safety and tolerability determined in healthy volunteers, CF and NCFBE patients	M57	No. The study has been terminated by Alaxia. An amendment to the Description of Work is in progress	CO	No
9	M9.4 Regulatory submission of phase IIa study in CF patients	M59	No. Preparation had commenced in the form of discussions with regulators regarding the device used to mix and administer the drug.The study has been terminated by Alaxia. An amendment to the Description of Work is in progress	CO	Yes. Minutes of meeting with regulators in UK and Sweden
10	M10.6 Regulatory approvals obtained	M49	Yes Regulatory approvals have been obtained in UK, Germany and Spain	CO	Yes. Letters of approval attached
10	M10.3 First patient first visit in Phase II trial of QBW251.	M69	Yes. First patient first visit has been completed	CO	Yes. Confirmation from TMC Pharma acting as CRO for this study
10	M10.4 Completion of enrolment in Phase II trial of QBW251.	M75	Not yet. Patient enrolment is ongoing. Currently projected to complete in M86	CO	Yes. Latest pack detailing study progress
11	M11.2 Transfer of registry samples from UNIVDUN to QUB	M67	Yes. Material Transfer Agreement has been signed and samples transferred	CO	Yes. Copy of Material Transfer Agreement

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

Work package 1

The COVID-19 pandemic continued to have an impact on the project plan during this period, in that many of the lab activities in both the academic and commercially contracted institutions dealt with a backlog of work as a result of restrictions. In addition, clinicians continued to manage COVID-19 patient priorities as several waves of infection were experienced across the EU. Despite these restrictions, each work package made their best efforts to continue work where possible. Team meetings were maintained where possible and the focus moved to re-assessing the plan and recovery.

The annual General Assembly meeting took place online in January 2021, which gave the partners an opportunity to catch up with progress made and to make plans for the year. Amendment #4 and amendment #5 were signed within this period. Amendment #4 confirmed the re-admission of Fundacio Clinic per a la Recerca Biomedica to the consortium and a change the work programme proposed by Polyphor AG. Amendment #5 again updated the Description of Work to take account of delays incurred due to the global pandemic which affected the availability of both clinicians and facilities. At the time of submission of the Y6 report, Amendment #6 is being written to reflect the changes incurred due to the announcement by Alaxia that they intended to terminate their ALX-009 programme.

Contracts for CRO services provided in WP8, WP9 and WP10 were extended and additional costs negotiated.

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

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 has surpassed 20,000 patients, which is double the original target.

Work package 7

During the previous period, an issue was discovered with the murepavadin formulation in storage. This necessitated a re-formulation of the drug to ensure adequate shelf life.

The drug product is an aqueous solution of murepavadin at pH 4, that when it is neutralized with the phosphate buffer at pH 13 produces a clear solution appropriate for nebulization at pH 7. The further dilution of this solution with 0.9 % NaCl solution to achieve lower concentrated doses, does not modify the targeted pH. The final Murepavadin solutions for nebulization will be administered using the eFlow® Nebulizer, which generates an aerosol of high Murepavadin content and a defined droplet size.

Murepavadin is presented as a concentrate for nebulizer solution with concentration of 50 mg/mL and nominal volume of 4 mL in 10R type I amber glass vials (Table 1). The concentrate is transformed into the nebulizer solution by two successive dilution steps: (1) with a basic phosphate buffer solution (basic solution) and (2) 0.9 % NaCl solution (saline). For the highest dose to be administered step (2) is not required. The clinical trial protocol of POL7080-201-01 study describes the dose and dose schedule foreseen in this study.

The basic solution is a phosphate buffer solution with a nominal volume of 4.7 mL and is provided in 5 mL cyclic olefin polymer vials (Table 1).

Table 1. Clinical Formulation

Formulation	Description/ Presentation	Dose Strength (mg)	Excipients[§]
Murepavadin			
Murepavadin solution *(Liquid formulation)*	Liquid solution	200 mg/vial *(50 mg/mL as net peptide)*	- Hydrogen chloride - Water for injection
Basic solution			
Phosphate buffer *(Liquid formulation)*	Liquid solution	-	- Sodium dihydrogen phosphate dihydrate - Sodium hydroxide - Water for injection

[§]All excipients used are of pharmacopoeial grade.

The available stability data of murepavadin (50 mg/mL) and the basic solution (phosphate buffer) support the storage in a refrigerator at 2°C to 8°C. The drug product sections of the Investigational Medical Product Dossier (IMPD) include the batch-specific instructions and the information on the storage conditions.

The solution for nebulization shall be prepared and transfer immediately to the reservoir of the PARI eFlow® nebulizer after its preparation. The Pharmacy Manual instructs on how to prepare and transfer the solution for nebulization to the PARI eFlow® nebulizer.

Murepavadin solution does not contain antimicrobial preservatives. Therefore, the solution for pulmonary administration must be prepared and handled with care to avoid microbiological contamination. The Pharmacy Manual provides further details on how to conduct the dilutions.

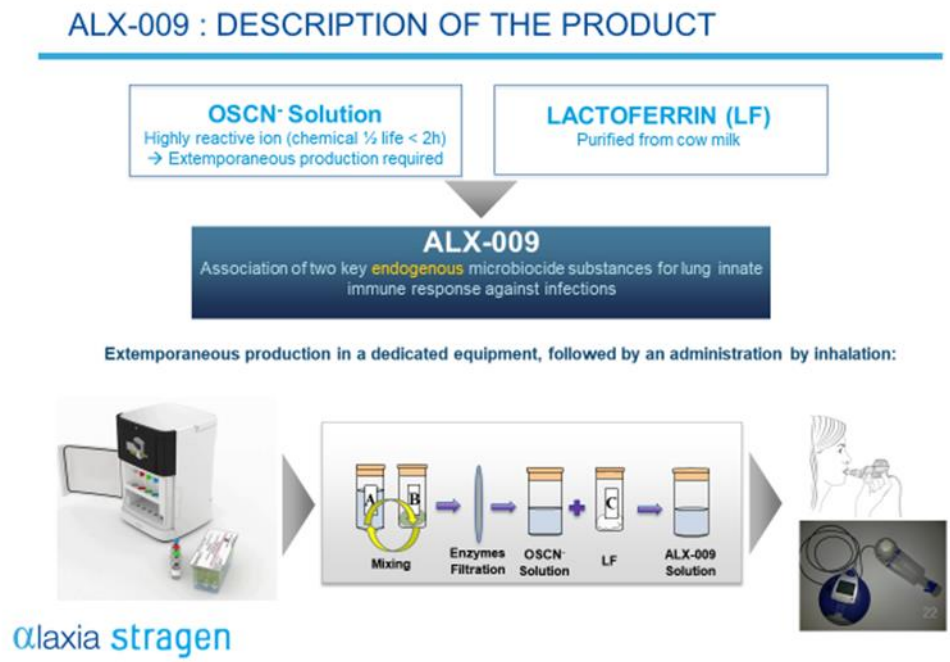
The solution for nebulization should be used immediately after its preparation. If not used directly, in-use storage times and conditions before use should not exceed 24 hours at 2 to 8°C and 3 hours at ambient temperature (15 to 25°C). The drug product sections of the Investigational Medical Product Dossier (IMPD) include more information on the storage conditions.

Work package 9

Discussions were held with two healthcare agencies, MPA Sweden and MHRA UK, regarding ALX-009 drug release using the EOLEASE machine at home. Both agencies confirmed that they were open to approving the current solution for clinical study Phase II in their respective countries.

The ALX-009 CMC program continued during this period. Production runs were completed under GMP conditions and the stability of the product studied. EOLEASE consumables were also modified in order to improve robustness and ensure ease of production. Minor leakage problems were resolved and software bugs have been corrected.

EOLEASE and its SUF Kit are also now considered as a Machine according to new EU 2021 Machinery Directive. This is a great achievement as the EOLEASE machine can now be CE marked under this regulation.



Work package 10

During this period, Trial Steering Committee meetings continued and clinical site initiation took place. A number of virtual Investigator meetings were held to advance training and encourage further recruitment. The TSC have also remained in contact with the arm of the study taking place in China, to share information and discuss recruitment queries.

Work package 11

Analysis of CT scans of previous studies stored in the EMBARC registry began. This activity was not previously captured in the Description of Work but was discussed and a plan of work developed during the period when the clinical studies outlined in WP8, WP9 and WP10 were delayed. This analysis will supplement the body of knowledge gathered in WP11.

Additionally, in WP11, genome sequencing of EMBARC samples has begun in this period. This activity although in the early stages is producing some exciting results in that some common genetic traits have been discovered.

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

Work package 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.

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 has been published. It was planned that further analysis of LCI data would be possible as a comparison of CT data. Since that time, the LCI study has been discontinued and the

investigator leading it has left the team. In light of these developments, the WP11 team plan to evaluate the possibility of completing this deliverable in the final period and will inform IMI of any changes.

Work Package 9

In the final month of this period, the iABC Management Board were informed by Alaxia of their intention to terminate the ALX-009 programme due to financial issues. The effect of this decision is that the Phase I study which had entered its final part in CF patients, will stop and no further development will take place. Deliverables D9.2, D9.3 and D9.4 are affected and will be updated in a planned amendment to the Description of Work.

Work package 10

M10.4 Completion of enrolment in Phase II trial of QBW251. As the study start-up was delayed due to the COVID-19 pandemic, recruitment to the QBW251 study is not yet complete. It is currently planned to complete in Q4 2022.

2.3 Deviations from Description of Work

There are no deviations from the Description of Work to report in this period. Amendments #4 and Amendment #5 to the Grant Agreement were approved during this timeframe and the work plan updated accordingly.

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 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 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 7

In vivo efficacy of Murepavadin in animal models

Efficacy studies showed that murepavadin efficacy driver is the fAUC/MIC and its intratracheal (IT) administration at low dose resulted in several log10 reduction of bacterial burden in the mouse lung infection model.

The intratracheal route of administration was chosen as a substitute to inhalation due to the limited availability of CROs able to perform both inhalation and efficacy studies in infection murine models. IT treatment was initiated 2 hours post challenge at different single doses and lung bacterial loads were quantified based on CFUs. A total of four P. aeruginosa isolates were tested with MICs ranging from 0.125 to 0.25 mg/L, including one CF strain BAA2113 (see reports PH7080-X0277 to PH7080-X0280).

Murepavadin formulation

The drug product is an aqueous solution of murepavadin at pH 4, that when it is neutralized with the phosphate buffer at pH 13 produces a clear solution appropriate for nebulization at pH 7. The further dilution of this solution with 0.9 % NaCl solution to achieve lower concentrated doses, does not modify the targeted pH. The final Murepavadin solutions for nebulization will be administered using the eFlow® Nebulizer, which generates an aerosol of high Murepavadin content and a defined droplet size.

Murepavadin is presented as a concentrate for nebulizer solution with concentration of 50 mg/mL and nominal volume of 4 mL in 10R type I amber glass vials. The concentrate is transformed into the nebulizer solution by two successive dilution steps: (1) with a basic phosphate buffer solution (basic solution) and (2) 0.9 % NaCl solution (saline). For the highest dose to be administered step (2) is not required.

The basic solution is a phosphate buffer solution with a nominal volume of 4.7 mL and is provided in 5 mL cyclic olefin polymer vials.

The available stability data of murepavadin (50 mg/mL) and the basic solution (phosphate buffer) support the storage in a refrigerator at 2°C to 8°C.

Inhalation toxicology reports (GLP toxicology studies in mouse (report PH7080-X0034) and non-human primate (report PH7080-X0035)

In support of the inhaled murepavadin development program, 14-day repeat inhalation dose range finding (DRF; non-GLP) studies and two GLP 28-day repeat inhalation dose regulatory toxicity studies have been completed in mouse and non-human primate to assess the systemic and local toxic potential of murepavadin. Recovery from any effects were evaluated after a 4 week recovery period. No clinical signs or organ toxicity

previously reported during the nonclinical studies conducted in support of the intravenous program were observed.

In the mouse, mean estimated achieved doses of 0.8, 3.5 and 7.3 mg/kg/day murepavadin free base were administered. Based on the results of this study there was no evidence of systemic toxicity up to 7.3 mg/kg/day murepavadin free base, however, due to adverse pathology in the upper respiratory tract, the No Observed Adverse Effect Level (NOAEL) could not be established.

Following inhalation administration of murepavadin to cynomolgus monkeys for 4 weeks, at mean estimated achieved doses of 1.5, 4.0 and 10.7 mg/kg/day murepavadin free base microscopic test item related findings were reported at the tracheal bifurcation of both sexes given 10.7 and 4.0 mg/kg/day, and also in one female given 1.5 mg/kg/day, but were not considered adverse and were not present in the recovery animals. There were no other findings considered test item related.

Maximum mean exposure AUC(0-24h) following inhaled administration to cynomolgus monkeys at the high dose level of 10.7 mg/kg/day, at which no organ toxicity was observed, was approximately 8-fold lower than that obtained at the NOAEL (16 mg/kg/day) in the intravenous 28-day toxicity study in monkey.

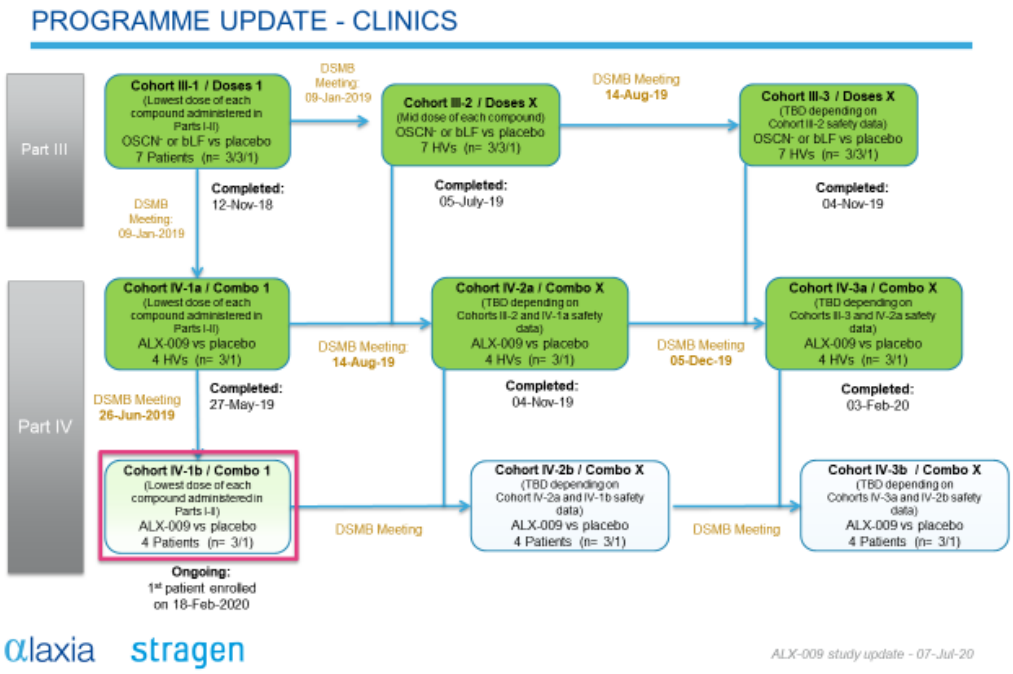
The outcome of the 28-day GLP toxicity study of inhaled murepavadin in mouse and NHP, in combination with all the non-clinical data generated and summarized in the POL7080 investigator brochure, allowed to move forward into clinical development.

Work package 8

The CTA was obtained from MHRA on December 18, 2020. In 2021, a substantial amendment was filed due to a CMC requirement for repackaging. The amendment was accepted on July 21, 2021. The first patient was dosed with inhaled murepavadin on December 14, 2021.

Work package 9

During this period, part IVb of the clinical study (depicted below) CF patients was initiated. One patient was randomised



The ECOLEASE machine used to provide the patient dose of ALX-009 was approved by regulators in UK and Sweden and can now go forward to apply for CE marking.

Work Package 10

The QBW251 study in BE patients is making good progress after delays due to the COVID-19 pandemic. Regulatory approval was gained in UK, Germany and Spain and 14 sites have now been initiated. Patient recruitment is continuing and at the time of report 10 patients have been randomised.

3.2 Key dissemination activities

Nature of Communication	Title	Responsible Participant (and presenter when relevant)	Date/location when relevant.	Target audience
Publication	Anti-biofilm activity of murepavadin against cystic fibrosis Pseudomonas aeruginosa isolates	Maria Diaz-Aguilar SERMAS	Journal of Antimicrobial Chemotherapy 2021; 76: 2578–2585 doi:10.1093/jac/dkab222 Advance Access publication 20 July 2021	Scientific and Clinical community
Publication	Murepavadin antimicrobial activity against and resistance development in cystic fibrosis Pseudomonas aeruginosa isolates	Maria Diaz-Aguilar SERMAS	Journal of Antimicrobial Chemotherapy 2021; 76: 984–992 doi:10.1093/jac/dkaa529 Advance Access publication 24 December 2020	Scientific and Clinical community
Abstract	Inhaled corticosteroids use in patients with bronchiectasis: Data from the EMBARC registry	Eva Polverino - VHIR et al	European Respiratory Journal 2021 58: OA1312; DOI: 10.1183/13993003.congress-2021.OA1312	Scientific and Clinical community
Publication	The impact of the COVID19 pandemic on exacerbations and symptoms in Bronchiectasis: a prospective study	Megan Crichton UNIVDUN et al	American Journal of Respiratory and Critical Care Medicine. https://doi.org/10.1164/rccm.202105-1137LE	Scientific and Clinical community
Abstract	The prevalence and impact of autoantibodies among people with bronchiectasis: a data analysis of the EMBARC registry	Michal Shteinberg et al	European Respiratory Journal DOI: 10.1183/13993003.congress-2021.PA2059 Presented at 2021 ERS International Congress	Scientific and Clinical community
Abstract	Long term clinical outcomes of bronchiectasis in India: Data from the EMBARC/RRNI Indian Bronchiectasis Registry	Raja Dhar et al	European Respiratory Journal 2021; 58: Suppl. 65, OA2855 DOI: 10.1183/13993003.congress-2021.OA2855 Presented at 2021 ERS International Congress	Scientific and Clinical community

Nature of Communication	Title	Responsible Participant (and presenter when relevant)	Date/location when relevant.	Target audience
Abstract	The microbiology of stable bronchiectasis: data from the EMBARC bronchiectasis registry	Michal Shteinberg et al	European Respiratory Journal 2021 58: OA1308; DOI: 10.1183/13993003.congress-2021.OA1308 Presented at 2021 ERS International Congress	Scientific and Clinical community
Abstract	Deteriorating heath status in bronchiectasis : longitudinal data from the EMBARC registry	Stefano Aliberti et al	European Respiratory Journal 2021 58: OA2853; DOI: 10.1183/13993003.congress-2021.OA2853 Presented at 2021 ERS International Congress	Scientific and Clinical community
Abstract	Characteristics and outcomes of adults with primary ciliary dyskinesia (PCD): an EMBARC/BEAT-PCD analysis	Amelia Shoemark et al	European Respiratory Journal 2021 58: PA2062; DOI: 10.1183/13993003.congress-2021.PA2062 Presented at 2021 ERS International Congress	Scientific and Clinical community
Abstract	Determinants of survival in the European Bronchiectasis Registry(EMBARC)	Stefano Aliberti et al	European Respiratory Journal 2019 54: OA4949; DOI: 10.1183/13993003.congress-2019.OA4949 Presented at 2021 ERS International Congress	Scientific and Clinical community
Publication	Validation of the Bronchiectasis Impact Measure (BIM): a novel patient-reported outcome measure	Megan Crichton - UNIVDUN et al	European Respiratory Journal 2021 57: 2003156; DOI: 10.1183/13993003.03156-2020	Scientific and Clinical community
Abstract	The Neutrophil Granule Protein Olfactomedin-4 Relates to Bronchiectasis Severity and Alters Mucociliary Clearance	M. Thompson et al	American Journal of Respiratory Critical Care Medicine 2021 Online abstracts issue ;203:A4400	Scientific and Clinical community
Publication	Diagnosis and quantification of bronchiectasis using computed tomography or magnetic resonance imaging: A systematic review	JJ Meerberg et al	Respiratory Medicine Volume 170, August–September 2020, 105954 https://doi.org/10.1016/j.rmed.2020.105954	Scientific and Clinical community
Publication	Criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults for use in clinical trials: international consensus recommendations	Stefano Aliberti et al	Lancet Respir Med 2022; 10: 298–306 Published Online September 24, 2021 https://doi.org/10.1016/S2213-2600(21)00277-0	Scientific and Clinical community
Publication	Shopping for phages? Unpacking design rules for therapeutic phage cocktails	Cedric Lood et al	Current Opinion in Virology Volume 52, February 2022, Pages 236-243 https://doi.org/10.1016/j.coviro.2021.12.011	Scientific and Clinical community
Publication	Evaluation of Rapid Polymyxin Pseudomonas test in clinical Pseudomonas aeruginosa isolates with various degrees of multidrug resistance	Javier Sanchez-Lopez et al	JAC-Antimicrobial resistance JAC-Antimicrobial Resistance, Volume 3, Issue 3, September 2021, dlab104, https://doi.org/10.1093/jacamr/dlab104	Scientific and Clinical community

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.

3.4 Overall management of the project

The management of the project continued in the same vein as period 5 with strong collaboration among the consortium. There was again some change within the consortium as amendment #4 and amendment#5 were implemented.

Throughout the year, the Coordination Unit met less frequently due to the availability of the team but Management Board continued once per month. Each of the work packages continued their meetings as appropriate and attendance and enthusiasm in all forums remains high.

The team had planned to convene for a GA in October 2020, but the surge in COVID-19 rates around that time again made it impossible for teams to travel. A virtual GA was held in January 2021 and it is planned that a similar session will be held in 2022.

Although previous plans to meet were put on hold, the consortium still plan to hold a brain-storming session early in period 7 to discuss future plans. There have been approaches from many EFPIA companies interested in pursuing projects.

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

All comments and recommendations highlighted in the P5 report have been noted by the consortium and addressed where necessary.

3.6 Project plan for the remaining reporting periods

Period 7 will primarily follow the Description of Work V5.0. Some changes will be made in the forthcoming amendment #6

Work Package 1

The focus will be on implementing the new Description of Work. As we enter the final period of the project, the consortium are hopeful that the restrictions placed by individual governments due to COVID-19 will begin to disappear allowing the programme of work to be completed. The request for amendment #6 to the Grant Agreement will be submitted to IMI in April 2022

Work Package 5

The focus continues to be on dissemination of the extensive data that is available from the registry. It is also hoped that further testing of EMBARC samples initiated in period 5 will yield more valuable information to add to the knowledge already gained.

Work Package 7

Work package 7 has largely been completed. The upcoming period will focus on the completion of Liposomal development.

Work Package 8

In this period, focus will be on achieving successful outcomes from the Phase I Murepavadin study. The Spexis team are at the time of report, considering the possibility of changing the final part of the current protocol from healthy subjects to CF patients. If a suitable protocol is agreed a further amendment will be requested.

Work Package 9

Work package 9 has been terminated following Alaxia's announcement, so no further activity will take place in the development of ALX-009

Work Package 10

Work package 10 will continue to focus on patient recruitment and the completion of the Phase II study.

Work Package 11

This work package will support the POL7080 and QBW251 clinical studies. In addition, the EMBARC registry samples will be tested at QUB. An additional focus will be placed on dissemination of results from this work package.

The following deliverables and milestones are planned

Deliverable number	Deliverable title	Work package	Nature	Planned delivery date
D7.6	Report on the effects of murepavadin enteral administration on lung flora and gastro-intestinal flora.	7	R	M89
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.	7	R	M90
D7.8	Report on WGS analysis.	7	R	M90
D7.9	Report on the development of breakpoints for P. aeruginosa in CF and for inhalation therapy.	7	R	M90
D7.11	Report on development of a liposomal formulation for inhalation	7	R	M89
D7.13	Report on swine studies PK/PD and efficacy.	7	R	M89
D7.14	Report on development of two-chamber formulation and device.	7	R	M89
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).	8	R	M95
D8.5	Data on new clinically relevant endpoints in HV such as microbiome analysis	8	R	M95

Deliverable number	Deliverable title	Work package	Nature	Planned delivery date
D10.3	Phase II trial of QBW251 in BE patients (abbreviated report of key outcomes).	10	R	M89
D10.4	Publication of study results	10	R	M95
D11.1	Quantitative sputum microbiology in clinical trials	11	R	M92
D11.2	Biorespository of clinical CF and BE respiratory isolates, linked to a database including microbial and patient information, for future research use	11	O (material &	M95
D11.3	Biobank of blood (BE) and sputum (CF & BE) samples, linked to a database including microbial and patient information, for future research use	11	O (material & database)	M95
D11.4	NGS microbiome analysis of samples collected in clinical studies (WP8, WP9, WP10) and comparison of exploratory molecular and conventional microbiological endpoints	11	R	M95
D11.5	Analysis of sputum inflammatory biomarker data collected in clinical studies (WP8, WP9, WP10) and comparison with conventional and other exploratory endpoints	11	R	M95

Deliverable number	Deliverable title	Work package	Nature	Planned delivery date
D11.6	Final Analysis of CT outcome measures: Cross sectional and longitudinal comparison of CT related outcome measures to spirometry and LCI outcome measures	11	R	M95
D11.7	PRAGMA-BE) analysis of volumetric chest CTs of BE patients	11	R	M95
D11.8	Microbiome analysis of EMBARC registry samples	11	R	M85

Milestone number	Milestone title	Work package	Planned delivery date	Nature
M7.6	In vivo testing of effect of oral / intratracheal administration of POL7080 on the microbiological lung flora and gastro-intestinal flora	7	M86	D7.6
M7.7	Development of the βENaC-Tg mouse model of chronic pulmonary infection and the use of this model for efficacy testing	7	M89	D7.7
M7.8	WGS analysis of CF and BE P. aeruginosa isolates completed	7	M89	D7.8
M7.9	Report on the development process of P. aeruginosa susceptibility breakpoints in inhalation therapy completed.	7	M89	D7.9
M7.12	Development of a Liposomal Formulation for inhalation completion	7	M84	D7.12
M7.13	Assessment of PK/PD and efficacy in swine completed	7	M90	D7.13
M7.14	Development of two chamber device completed	7	M90	D7.14
M8.4	Last patient last visit in Phase I study of POL7080 in CF patients.	8	M86	Email confirmation from CRO

Milestone number	Milestone title	Work package	Planned delivery date	Nature
M8.5	Safety, pharmacology and maximal tolerated dose of POL7080 in healthy subjects determined.	8	M89	Results from data analysis available in form of figures and listings, written dosing rationale for MTD available, interim safety report available
M8.6	Tolerable dose of POL7080 in HV adults determined.	8	M89	Results from data analysis available; report effective and tolerable dose available
M8.7	Completion of Phase I study of POL7080 in HV patients.	8	M89	D8.2
M10.4	Completion of enrolment in Phase II trial of QBW251.	10	M75	CRO report received
M10.5	Completion of the Phase II QBW251 study (LPLV).	10	M82	CRO report received
M11.3	Metagenomic analysis of inhaled antibiotic	11	M84	D11.4
M11.4	Sputum proteomics analysis and biomarker	11	M72	D11.5
M11.5	Completed resistome study	11	M81	D11.4
M11.6	Completion of whole exome sequencing and	11	M81	D11.4
M11.7	Dissemination of integrated bronchiectasis genomic studies	11	M92	Presentation at ERS annual congress/World Bronchiectasis congress
M11.8	Completion of sputum inflammatory biomarker analysis of samples from	11	M92	D11.5

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

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
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	Ongoing
WP8 Planned amendment to Protocol is not accepted	L	H	Protocol continues as currently planned	Spexis	Clear communication with regulatory authorities	Q4 2022
WP8, WP10 CTAs not accepted and/or revisions are asked for	M	M	Answer questions quickly and adapt CTA	Spexis, Novartis	Situation to be monitored	Ongoing
WP8, 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

Tel +32 (0)2 221 81 81 • Fax +32 (0)2 221 81 74 | infodesk@imi.europa.eu • www.imi.europa.eu • twitter: @IMI_JU
Postal address: IMI JU • TO56 • 1049 Brussels • Belgium | Visiting address: Ave de la Toison d'Or 56-60 • 1060 Brussels • Belgium