Periodic Project Report
Inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis
iABC

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Period 08/2018 – 07/2019
Reporting Period 4
Description of work - DoW v2.0

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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: ..... **Novartis Pharma AG**
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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 19 partners in 8 countries, 2 pharmaceutical EFPIA member companies 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 objectives outlined below

1. To determine the therapeutic efficacy of Tobramycin inhaled powder (TIP) in BE patients
2. To explore novel endpoints (microbiome, LCI and CT imaging) for clinical trials in both CF and BE
3. To build repositories of clinical respiratory isolates and sputum biobanks for use in future research
4. 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.
5. Study the formulation of Murepavadin (POL7080) in a preclinical setting to support the clinical development of inhaled therapy in patients with CF
6. Establish the pharmacology, DMPK and non-clinical safety of POL7080
7. Support the clinical development of inhaled POL7080 against respiratory infections with Pseudomonas aeruginosa (including multidrug resistant) in patients with CF.

Overall deliverables of the project

To achieve the objectives, the programme has been subdivided into 6 WPs each with specific deliverables which are summarised below:

- WP1 implements the management structure to handle the administrative, legal and financial aspects of the project
- WP4 supports the clinical development of TIP for patients with BE. Three studies of the efficacy and safety of tobramycin in BE patients with a history of exacerbations and chronic Pa infection will be performed: a Phase II dose finding study followed by a Phase III confirmatory programme.
- WP5 will develop an EU-wide registry for BE and aim to provide comprehensive data on the epidemiology, natural history and management of BE in Europe.
- WP6 will define 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. Exploratory endpoints studied will include microbiome analysis, LCI, sputum inflammatory biomarkers and chest CT imaging. In addition, quantitative sputum microbiology will be performed to determine changes in sputum density/resistance of Pa and other pathogens in clinical studies where relevant.
- 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 and then a Phase Ib/2a study in CF patients will be performed to determine a tolerable dose and generate safety, pharmacology and first efficacy data.

Summary of progress versus plan since last period

This is the fourth periodic report of the iABC consortium. Year four began with the 3rd General Assembly meeting which took place in Paris on September 19th 2018. Throughout this period the consortium has continued to make progress against the aims of the project while managing another period of change. At the beginning of this period, Novartis announced that the worldwide rights to commercialize TOBI Podhaler® (tobramycin inhalation powder) had been acquired by Mylan. This necessitated changes to both WP4 and WP6 and re-planning of the overall iABC project budget. WP4 completed the iBEST1 study of inhaled TIP in BE patients although recruitment was curtailed to 107 patients instead of the planned 180. Initial data from the trial appears positive and full publication of the results is planned in December 2019. WP6 continued to support IBEST1 with exploratory endpoint testing and it is anticipated that informative scientific results will also be published at the end of 2019. However, the shortfall in the planned project output, prompted the consortium to issue a call for submission of proposals from prospective new partners at the beginning of October 2018. A number of interesting programmes were among the submissions received but the Management Board decided that the studies proposed by Alaxia had the most synergy with the aims of the project. In parallel, Novartis proposed to add a Phase II QBW251 study to the project. The development of these two new programmes represented a significant portion of the Y4 output. The resulting request for amendment which was submitted to IMI in May 2019 included three new work packages, 9, 10 and 11. The POL7080 programme continued to progress well towards clinical trial during this period with substantial pre-clinical testing completed according to plan in WP7 and preparations for the Phase I studies at an advanced stage in WP8. In addition, several high value subcontracts were successfully awarded as a result of collaborations between the legal and procurement teams at Polyphor, UMCU and QUB. WP5 has continued to build on the tremendous success in establishing the EU registry. Patient registration at the end of this period stands at over 17,000. Academic interest in the data continues to grow with a considerable number of papers emerging this period. The focus of this work package will now move from recruitment of patients to the analysis of the data and patient samples already obtained. WP11 was established to carry out this body of work and the team are anticipating significant scientific outputs. In advance of the adoption of amendment number two to the description of work, the consortium have begun preparation for the proposed new bodies of work. Trial Steering Committees have been assembled and study protocol discussions have begun. The consortium continues to work well as a team and look forward to meeting for the 4th General Assembly in Madrid on September 27th 2019.

Significant achievements since last report

Key achievements this period include:-

- The EU Bronchiectasis registry has to date recruited over 17,200 patients in 33 countries, providing an invaluable resource for academic and clinicians. Each patient record has 8 pages of information, totalling 20-30 data points. There are now 11,000+ patients with 1+ years of data. Dissemination activities are also ramping considerably.
- The Novartis sponsored iBEST-1 Phase II clinical study was concluded with 107 patients enrolled. Database lock was achieved in May 2019. Initial analysis of the results is very positive and the final Clinical Study Report will be published in December 2019.
- The pre-clinical toxicology testing programme of the Polyphor IMP POL7080 has progressed according to plan. Formulation and stability testing have been successfully completed and toxicology testing is ongoing, with no issues encountered thus far. Whole genome sequencing and analysis of 1000 CF and BE pathogens has also been completed

- A protocol for the Polyphor sponsored POL7080 Phase 1 clinical study has been developed and a Clinical Research Organisation (CRO) has been appointed as a result of an EU tender procurement process. The study is on track to begin recruitment in Q1/Q2 2020.
- In WP1, a call was launched to find new programmes of work to further advance the aims of the programme. The proposal judged to be most compatible with the current programme of work has been developed into WP9. The amended Description of Work has been submitted to IMI for approval. The new DoW also includes:
    - A Novartis sponsored Phase II study with their CFTR Potentiator QBW251 in BE patients. (WP10)
    - A new programme of work, WP11 developed to build on the success of the EMBARC registry by beginning to analyse the samples and data gathered.

2 Summary of progress against objectives

2.1 Summary table

Work - Package	Milestone/ Deliverable (number and short title)	Date Due (Annex I- description of work)	Completed (Yes/Not yet/Partially)	Dissemin. level[1]	Related document attached (Yes/No/Not applicable)
4	D4.2 Phase II trial of TIP in BE patients (abbreviated report of key outcomes).	M35	Not yet – planned M56. The Clinical Trial Report from the CRO is available in first draft form but further narratives have been requested for completion. The team plans to release all trial	N/A	No
4	D4.3 Regulatory advice for Phase III trial of TIP in BE patients	M39	No – This Phase III trial and deliverable have been cancelled due to commercial decisions	N/A	No
6	D4.7	M44	Yes – the study has been accepted for publication in Pulmonary Pharmacology & Therapeutics. Vol 58 in October 2019 & paper available on iABC website	PU	Yes – 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.	M35	Not yet – planned M56 in line with the publication of the full Clinical Trial Report for iBEST1	N/A	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.	M35	Not yet – planned M56 in line with the publication of the full Clinical Trial Report for iBEST1	N/A	No

[1] PU = Public, fully open, e.g. web CO = Confidential, restricted under conditions set out in Model Grant Agreement CI = Classified, information as referred to in Commission Decision 2001/844/EC.

Work - Package	Milestone/ Deliverable (number and short title)	Date Due (Annex I- description of work)	Completed (Yes/Not yet/Partially)	Dissemin. level[2]	Related document attached (Yes/No/Not applicable)
6	D6.11 Final Analysis of Phase II TIP CT outcome measures: Cross sectional and longitudinal comparison of CT related outcome measures to spirometry and LCI outcome measures.	M35	Not yet. This activity was delayed in line with the iBEST1 clinical trial and is now proposed as part of WP11 in the recently submitted amendment.	N/A	No
6	D6.13 Automated measurements of airway-artery dimensions for BE patients	M42	Not yet. This activity was delayed in line with the iBEST1 clinical trial and is now proposed as part of WP11 in the recently submitted amendment.	N/A	No
6	D6.14 PRAGMA-BE analysis of volumetric chest CTs of BE patients.	M48	Not yet. This activity was delayed in line with the iBEST1 clinical trial and is now proposed as part of WP11 in the recently submitted amendment.	N/A	No
6	D6.15 Analysis of sputum inflammatory biomarker data collected in Phase 2 TIP dose finding study and comparison with conventional and other exploratory endpoints	M35	Not yet. This activity was delayed in line with the iBEST1 clinical trial and is now proposed as part of WP11 in the recently submitted amendment.	N/A	No
7	D7.1 Report on the development of POL7080 as a nebulized formulation for inhalation therapy	M38	Yes	CO – may be public at a later stage	Already accepted on SOFIA
7	D7.2	M48	Yes	PU	Yes – added to SOFIA

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Work - Package	Milestone/ Deliverable (number and short title)	Date Due (Annex I- description of work)	Completed (Yes/Not yet/Partially)	Dissemin. level[3]	Related document attached (Yes/No/Not applicable)
7	D7.3	M42	Yes	PU	Yes – added to SOFIA
7	D7.5 Inhaled POL7080 efficacy results of in vivo testing in acute infection models	M48	Partially – activity is ongoing but not expected to report until M70	N/A	No
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.	M48	Partially – activity is ongoing but not expected to complete until M77	N/A	No
4	M4.5 Completion of enrolment in Phase II trial of TIP	M27	Yes. As Novartis divested TOBI Podhaler® to Mylan in August 2018. The iBEST1 trial ceased recruitment with 107 patients	PU	Yes. Letter from CRO ICON to confirm the closure of the study attached.
4	M4.6 Last Patient last visit in the Phase II TIP study	M35	Yes. Last patient last visit was completed in M44, March 2019	PU	Yes. Confirmation email from ICON attached
4	M4.7 Regulatory discussions prior to Phase III trial	M39	No- This Phase III trial and milestone have been cancelled due to commercial decisions	N/A	No
4	M4.8 First patient first visit in Phase III trial of TIP	M47	No- This Phase III trial and milestone have been cancelled due to commercial decisions	N/A	No
6	M6.1 Exploratory molecular endpoints to measure changes in composition of the airway microbiome/resistome determined.	M35	Not yet – planned after M56 with the publication of iBEST1 results	N/A	No

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Work - Package	Milestone/ Deliverable (number and short title)	Date Due (Annex I- description of work)	Completed (Yes/Not yet/Partially)	Dissemin. level[4]	Related document attached (Yes/No/Not applicable)
6	M6.5 Validation of LCI as a meaningful secondary exploratory outcome measure in Phase II TIP BE study (WP 4B).	M35	Not yet – planned after M56 with the publication of iBEST1 results	N/A	No
6	M6.7 Websites for standardization of chest CTs in Phase II and III studies.	M35	Yes. Testing was completed Q1 2019. The website is live and can be utilized for a clinical trial after a performance check ('pilot study').	PU. Website will be open to visit for everyone but a personal account is necessary for access to study information	Link to the website
6	M6.8 BE Scoring baseline CTs: Image analysis baseline Phase II (Bauman and Hartmann scoring, PRAGMA-BE).	M57	Partially. Hartmann, Bauman and PRAGMA-BE (BEST-CT) image analysis methods are completed and data are in the database.	PU. Paper is in progress	Not yet. Paper will be forwarded as soon as completed.
6	M6.9 Exploratory sputum inflammatory biomarker endpoints determined	M35	Not yet – planned after M56 with the publication of iBEST1 results	N/A	Not applicable
7	M7.1 Preliminary report the optimal conditions for nebulization of POL7080 as an inhalation therapeutic, with an adequate nebulization device. Decision on whether to proceed to actual development and to inhalation toxicology.	M36	Yes	CO	Yes – report on SOFIA

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Work - Package	Milestone/ Deliverable (number and short title)	Date Due (Annex I- description of work)	Completed (Yes/Not yet/Partially)	Dissemin. level[5]	Related document attached (Yes/No/Not applicable)
7	M7.2 Report on feasibility of POL7080 as DPI.	M48	Yes	PU	Yes. D7.2 added to SOFIA
7	M7.3.1 In vitro microbiological testing of POL7080 activity against Pa from CF and BE patients completed.	M36	Yes	PU	Yes. D7.3 added to SOFIA
7	M7.3.2 MICs and MBCs raw data available to establish adequate dosage in animal model.	M34	Yes	PU	Yes. D7.3 added to SOFIA
7	M7.4 Biofilm testing of POL7080 activity against CF pathogens completed. Including development of BioFlux system for susceptibility testing	M48	No – testing is ongoing and now expected to complete M66	N/A	No
7	M7.5 In vivo efficacy testing of POL7080 activity against CF p.aeruginosa isolates in acute infection model completed.	M42	Partially – activity has begun and is ongoing, but not expected to report until M70	N/A	No
7	M7.6 In vivo testing of effect of oral/intratracheal administration of POL7080 on the microbiological lung flora and gastro-intestinal flora	M48	No – this activity has been delayed. Delivery now expected M66	N/A	No
7	M7.7 Development of the βENaC-Tg mouse model of chronic pulmonary infection and the use of this model for efficacy testing	M42	No – this activity has been delayed. Delivery now expected M66	N/A	No

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Work - Package	Milestone/ Deliverable (number and short title)	Date Due (Annex I- description of work)	Completed (Yes/Not yet/Partially)	Dissemin. level[6]	Related document attached (Yes/No/Not applicable)
8	M8.1 Formation of trial steering committee	M48	Yes	PU	Yes. TSC team charter and minutes of first meeting attached.

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

Work package 1

The Novartis decision which was announced at the beginning of this period, required analysis of the overall project and associated budget. The consortium Management Board (MB) took the decision to launch a call for proposals from parties interested in joining the programme. The call which was disseminated through the BEAM Alliance and EFPIA networks, resulted in many expressions of interest and five proposal submissions. The submissions were analysed and discussed by the MB and they voted to pursue the proposal from Alaxia SAS. Work continued with the Alaxia team throughout Q1 and Q2 2019 to develop a newly proposed work package 9. In parallel Novartis proposed a new programme of work to replace the TIP studies. Considerable work was also undertaken to develop this into the proposed work package 10. Work has continued on both work packages 9 & 10 to align them with the overall project plan in anticipation of amendment approval by IMI.

In November 2018, representatives of the iABC consortium met with IMI and external reviewers to carry out a mid-project review. The group found this a very useful exercise and helped direct how the latest project amendment was framed. A key point raised by the reviewers was the lack of outreach or dissemination of the project and one of the actions taken to address this was the update of the iABC website with a new look and feel and updated content. Dissemination activities have also dramatically increased during this period, particularly building on the success of the work package 5 EMBARC registry.

Work package 4

The iBEST1 clinical study was concluded in March 2019 and database lock was achieved in May 2019. The Novartis team have been working with the TSC and the CRO ICON to clean and analyse the results. The initial view is that the results look positive. A draft Clinical Study Report (CSR) has been made available in September 2019, but the final analysis is expected to be published in December 2019

Work package 6

Sputum microbiology and susceptibility testing: Academic partners at Antwerp and QUB developed a central laboratory microbiology manual which was used in the Phase II TIP iBEST-1 study. The central laboratory in Antwerp received a total of 1440 samples from 107 patients as follows:

- 630 sputum samples for quantitative microbiology

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- 607 sputum samples for inflammatory biomarkers
- 98 Swabs for microbiology
- 105 Swabs for NGS and/or additional analysis

An initial aliquot of all 630 sputum samples was processed for quantitative sputum microbiology with 98 swabs processed for semi-quantitative sputum microbiology. Any remaining sample was divided and aliquots processed for inflammatory biomarker measurement or snap frozen for next-generation sequencing analysis. In total, 7339 aliquots (N=6613, inflammatory biomarker measurement; n=726, next -generation sequencing) were prepared and sent to Belfast for further analysis with a further 545 samples (all sputum) biobanked in Antwerp.

P. aeruginosa isolates (n=672) have been cultured from sputum (n=659) and swabs (n=14) with 163 additional BE pathogens also detected. These were: *S. aureus*, n=58; *A. xylosoxidans*, n=22; *H. influenzae,* n=14; *S. maltophilia,* n=14; *S. pneumoniae*, n=7; *Klebsiella spp.*, n=7; *M. catarrhalis*, n=2; *Proteus spp.,* n=2. Antimicrobial susceptibility of tobramycin, aztreonam, ceftazidime, ciprofloxacin, colistin, imipenem, meropenem and piperacillin/tazobactam has been determined for 627 *P. aeruginosa* isolates with 35 *P. aeruginosa* isolates having no result for imipenem due to failed QC (issue with Cation adjusted Mueller-hinton broth W/TES from supplier). To date, 898 (226 additional *P. aeruginosa* morphological types after frozen storage discovered during MIC testing) *P. aeruginosa* and additional BE pathogens isolates have been stored at -80°C.

Molecular analyses as exploratory endpoints to measure changes in composition of the airway microbiome and resistome: Standardized protocols have been developed for DNA extraction, PCR and next-generation sequencing (NGS). Initial experiments comparing qPCR vs. quantitative culture for *P. aeruginosa* in pure culture demonstrated a good correlation. Using excess expectorated sputum samples collected from adult CF patients, total bacterial and *P. aeruginosa* load in CF sputum has also been compared using qPCR and quantitative culture with a good correlation observed. CF sputum samples were also analysed by NGS to enable comparison between relative abundance of *P. aeruginosa* and *P. aeruginosa* load measured by qPCR and culture. The qPCR assay has been used to determine both total bacterial and *P. aeruginosa* load in a large biobank of sputum samples (>1000) collected in previous clinical studies; these samples have already been analysed by NGS and we are currently determining if there is a correlation between *P. aeruginosa* load and relative abundance. Six hundred and ninety-two samples received from Antwerp have been processed for microbiome analysis: 621 sputum samples and 71 swab samples. All sputum samples have been processed with protocols currently being adapted for DNA extraction from swabs. All sputum samples have been sequenced with data analysed ongoing but not linked with patient identifiers.

LCI as an exploratory endpoint:

Development of LCI Training programme, eLearning tool (www.MBWtraining.com) and a central LCI reading service in QUB has been completed. Development and finalisation of associated local protocols and SOPs for this activity (LCI training and central over-reading) was also completed in parallel.
Training was completed in 20 sites taking part in LCI sub study where a training need was identified.
The certification process (central over-reading of n=10 tests) was completed in 13 sites under the guidance of the Belfast centre. Evaluation and write-up of the training and certification programme is ongoing.
From commencement until the end of the iBEST-1 study, LCI testing and submission of LCI data has been completed for 236 tests (n=40 participants in 11 sites).
Central over-reading and double over-reading (quality assurance) has been completed for all 236 tests. All data submission and reconciliation steps have been completed with the sponsor and CRO, prior to database lock.

The following analysis and dry run efficacy outputs have been complied for review:

- Tables, listings and figures compiled for change in LCI from baseline and shift tables in lung clearance index at each post-baseline visit (presented with standard descriptive statistics [n, mean, SD, minimum, median, and maximum] by cohort and treatment arm).
- LCI responder table generated: Pre-dose FEV% by LCI responders at each visit.

Further data analysis as per protocol is planned.

Analysis of sputum inflammatory biomarker data and comparison with conventional and other exploratory endpoints:

The following inflammatory biomarkers were analysed in the sputum supernatants received from Antwerp; Elastase, IL-8, IL-1b, HMGB-1 and Calprotectin. IL-8 and IL-1b were analysed using the Simple Plex cartridges run on the Ella platform (ProteinSimple, United States) following the manufacturer's instructions. HMGB-1 and Calprotectin were measured by commercially available ELISAs according to manufacturer's instructions (IBL International, Germany and Fine Test, Wuhan Fine Biological Technology Co., China respectively). Free neutrophil elastase (NE) activity was measured by a colorimetric microtitre plate assay, using the elastase substrate N-Methoxysuccinyl-Ala-Ala-Pro-Val-pNitroanilide (Elastin products, United States). In total 606 sputum samples were tested and the final results database sent to ICON on 03 Jun 2019.

Work package 7

In addition to the activities recorded as deliverables and milestones, a number of important supplementary activities were conducted as per the Description of Work in preparation for the POL7080 Phase I clinical study.

Pre-clinical inhalation toxicology (subcontracted)

An extensive EU tender process was undertaken by UMCU to procure pre-clinical inhalation toxicology testing services. The contract was awarded to Envigo (Envigo was recently taken over by LabCorp/Covance, hence now called Covance) in December 2018 and testing began in January 2019. Dose-range finding studies and (GLP-compliant) 28-day studies in the mouse as a rodent and the monkey as a non-rodent model were planned. To date the results of the 14-day escalating dose in mice were received at end of July 2019 and the inhalation results at the end of August. The non-rodent testing is progressing well with final results expected in November 2019.

Whole genome sequencing analysis

The data generated from whole genome sequencing (WGS) of 1000 pathogenic strains from CF and BE strains were continued to be analyzed at UMCU and SERMAS-HURYC. Comparative genetic analysis of *H. influenzae* strains and Pandoraea species was completed and submitted for publication, as was the analysis of a number of unique isolates. Proposals for re-organization of taxonomic classification of some emerging CF-pathogens were made based on these analyses. Analysis on *Burkholderia*, *Pseudomonas aeruginosa, Stenotrophomonas and Achromobacter* is ongoing.

Chemical stability testing and liposomal formulation

The initial pre-clinical testing results are showing positive results to date

Bachem AG, with whom Polyphor have an ongoing Master Service Agreement were awarded the contract to develop a method and test to ensure the absence of *S. aureus*, *P. aeruginosa* and bile-tolerant, gram-negative bacteria in POL7080.

Interlabor AG were contracted to perform a stability study on nine formulations of POL7080. Samples were analysed at T0, T1, T2 and T4 weeks stored at 5, 25 and 40 degrees Centigrade for appearance, purity and related substances

Pari AG carried out testing on physicochemical characteristics and aerosol performance data with two different formulations of POL 7080 upon nebulisation utilizing an eFlow nebulizer. pH, osmolality, viscosity and surface tension of two formulations were determined at three timepoints (T0, T1 and T4 (weeks)) and two storage temperatures (2-8°C and 25 °C). TOR and MMD were determined by laser diffraction measurements utilizing an investigational eFlow with two different head types (class 30 and 40). Based on these results an eFlow configuration was chosen for further measurements. Aerodynamic Particle size distribution (APSD) was determined by impactor measurements (NGI) utilizing the agreed on eFlow configuration (class 30 head or 40).

During a long term stability program of the selected formulation, aerosol characteristics of samples stored at two temperatures (2-8°C and 25°C) was determined by Next Generation Impactor measurements at eight timepoints (T0, T1, T3, T6, T9, T12, T18, T24 (months)).

An EU tender process was undertaken to procure a liposomal formulation development service. The contract is currently in negotiation with Polymune AG and is anticipated to begin in October 2019. Liposomal formulation could show a potentially improved tolerability and improved biofilm penetration.

Work package 8

This work package supports the Phase I clinical trials demonstrating the pharmacology and safety of POL7080 in healthy volunteers and CF patients infected with Pa. The first study is due to begin in Q1 2020 so the preparation began during this period. A Trial Steering Committee was convened to begin working on the study protocol. At the time of submission of this report, the protocol is in an advanced stage.

An EU tender process was undertaken to procure a CRO to manage the clinical trials. The tender submissions are currently in review with a view to awarding the contract early in November 2019.

Although the following work packages are not currently fully approved as part of the new DoW (v3.4), some work began to prepare for their addition

Work package 9

Alaxia SAS are a new partner to the iABC consortium and at the time of their application to join the project, their programme of work (Phase I study) had already begun. Should the amendment to the DoW be approved by IMI, it is planned that the cohorts in parts III-2, III-3, IVa and IVb will become part of the project. To oversee and advise on these activities a TSC has been assembled and protocol development is at an advanced stage. Discussions have also begun on CRO procurement.

Work package 10

This work package contains the Novartis QBW251 Phase II clinical study. The planned study contains two arms, one in EU, which it is proposed will form part of the iABC project, and an arm which will be conducted in China. To develop the protocol a joint TSC between the EU and China academics and clinicians has been formed and have met regularly since April 2019. A face to face planning meeting is tabled at the consortium General Assembly meeting which will take place on Friday 27th September 2019 in Madrid. The protocol has been agreed and is currently in final quality review at Novartis. The EU tender process to procure a CRO to manage the EU part of the trial is in development.

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

Work package 6

M6.7: Website for standardization of chest CTs in Phase II study:

The requirements for the interactive website have resulted in a more complex structure than was anticipated. To ensure a safe, high quality and site- and study-specific environment, a standard web building program was not suitable. Erasmus MC contracted a company to construct a functional website and deliver overall design. For studies that include chest CT, the website will be essential for standardizing, certifying the CT scanning protocols and enabling monitoring of CT scans made for a study. Currently the website is active on a secure Erasmus MC server. Erasmus MC-LungAnalysis have backend control for data input. Functionalities and maintenance services is done under contract to the company who constructed the website. The Website can be used for upcoming iABC studies.

M6.8: BE Scoring baseline CTs: Image analysis baseline Phase II (Bauman and Hartmann scoring, BEST-CT (based on PRAGMA-CF).

Analyses of the CT scans was started directly all available CT scans were received. Image analysis using 3 semi-quantitative scoring methods (Baumann, Hartmann and the BEST-CT (based on PRAGMA-CF)) was initiated and completed. Statistical analysis and writing a paper describing the results is currently ongoing.

Deliverable D6.13 Automated measurements of airway-artery dimensions for BE patients: will be 18 months after date of last patient last visit. Currently the manual annotations and development of the automatic AAratio measurement algorithm are in progress.

Deliverables D6.4 and D6.9 have been delayed to month 56 to match deliverables for the iBEST-1 study (study abbreviated outcomes and publication of results) and allow detailed comparison of novel and conventional endpoints.

Work package 7

Deliverables/milestones D7.5, D7.6 and D7.7 are delayed. D7.5 and D7.7 are ongoing, D7.6 will start shortly. Initial planned timelines were too tight and these have been adapted in the new Description of Work to run longer. The extension of the project will allow in particular for more extensive and robust development of the βENaC-Tg mouse model (D7.7) and a higher degree of analyses of the whole genome sequence data without increase in required budgets.

2.3 Deviations from Description of Work

Most of the deviations from the DoW which occurred in this period were as a result of the changes in work package 4. In addition to the removal of the planned Phase III study with inhaled TIP, there was a knock-on effect on work package 6 in that the planned work to support both the Phase II (iBEST) study and the Phase III were also made redundant. These changes have necessitated the overall planning of the iABC project and a request for amendment to the DoW was submitted to IMI in May 2019.

Work Package 4

Study was initiated in Feb-2017; 107 patients (out of 180 planned) were been recruited at 36 sites in 7 countries. Recruitment was significantly behind target and the challenges in recruitment were presented in the annual report 2018 (Y3).

On 31 August 2018, the worldwide rights to commercialize TOBI Podhaler® (tobramycin inhalation powder) were acquired by Mylan. As Novartis no longer owns TOBI Podhaler®, the recruitment of new patients into the ongoing Phase IIB CTBM100G2202 study iBEST-1 was closed earlier than planned. The WP4 Trial Steering Committee and consortium partner were informed and planning initiated to ramp the study down. All patients who signed informed consent and entered screening, were offered the possibility to continue the study. The Last patient last visit (pt 107) occurred on 20-Mar 2019. All relevant data from the study will be analysed and shared as per iABC publication plan and Novartis data disclosure policy.

As consequence, the milestone D4.2 (Phase II trial of TIP in BE patients - report of key outcomes) is planned to M56 (Dec 2019).

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 it's Description of Work.. Despite this period of change, the consortium are pleased to report that valuable progress continued to be made. The following are the highlights of the period.

- The Data Monitoring Committee met on 21 August 2018 to review the iBEST1 study. No safety issues were identified and the committee recommended to continue the study with no modifications
- Last Patient Last Visit on the iBEST1 clinical study was achieved on 20th March 2019 and database lock occurred on 21st May 2019. The final study report is due to be published in December 2019.
- The iBEST1 clinical study design was accepted for publication in Pulmonary Pharmacology & Therapeutics.
- Completion of all sputum microbiology and antimicrobial susceptibility testing in the iBEST-1 study.
- Completion of all sputum inflammatory biomarker analysis in the iBEST-1 study.
- Extraction of DNA and next-generation sequencing (Illumina Miseq) of all sputum samples in the iBEST-1 study.
- 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.
- The EMBARC registry currently has 17000 patients enrolled into the study, from 30 countries. This far exceeds the original estimates and makes the EMBARC registry the largest such data resource in the world. Initial analysis of the data shows that the data is representative, with demographics, treatment patterns and severity characteristics which are in keeping with what is already known about bronchiectasis in Europe.
- EMBARC 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.
- Development of a new grid annotation image analysis method for quantitative analysis of CT scans from bronchiectasis patients completed.
- Development of a website for site certification for a clinical trial that has CT scanning as an outcome measure. E-training modules and CT procedure monitoring and CT scan feedback tools are included in this website.
- Testing of different nebulized and dry powder formulations of POL7080 completed
- Whole genome sequencing of The 1000 CF and BE pathogens collected for WP2 and WP7 has been completed: to include Pseudomonas aeruginosa, Burkholderia cepacia complex, Stenotrophomonas maltophilia, Achromobacter xylosoxidans, Haemophilus influenzae, Pandoraea, Ralstonia and Enterobacteriaceae. The availability of whole genome sequence data makes it a possibility to assess the breadth of activity of a compound within a species and informs about potential resistance mechanisms.

3.2 Key dissemination activities

Nature of Communication	Title	Responsible Participant (and presenter when relevant)	Date/location when relevant.	Target audience
Poster presentation	A randomised placebo-controlled dose finding study of tobramycin inhalation powder (TIP) in patients with bronchiectasis (BE) and pulmonary P. aeruginosa (Pa) infection	Michael Loebinger and Gerhild Angyalosi	17-Sep 2018 ERS, Paris	Scientific community, patients organisations
Abstract presentation	In vitro antimicrobial activity of tobramycin, colistin, aztreonam and the new antibiotic POL7080 against cystic fibrosis *Pseudomonas aeruginosa* biofilms	Maria Diez Aguilar SERMAS-HURYC	IMI 10th anniversary scientific symposium. October 2018, Brussels	IMI researchers
Manuscript (study design)	Efficacy and safety of tobramycin inhalation powder in bronchiectasis patients with P. aeruginosa infection: Design of a dose-finding study (iBEST-1)	Michael Loebinger	Pulmonary Pharmacology & Therapeutics. Due Oct 2019	Scientific community, patients organisations
Publication journal, Microbiol Resour Announc	Draft Genome Sequence of Haemophilus haemolyticus Strain 16/010 O, Isolated from a Sputum Sample from a Cystic Fibrosis Patient.	UMCU	Jun 2019	Clinical microbiologists
Publication journal, Int J Antimicrob Agents	Antimicrobial susceptibility of non-fermenting Gram-negative pathogens isolated from cystic fibrosis patients.	SERMAS-HURYC	Jan 2019	Clinical microbiologists

Nature of Communication	Title	Responsible Participant (and presenter when relevant)	Date/location when relevant.	Target audience
Abstract	New isolation of non-tuberculous Mycobacteria in patients with bronchiectasis- data from the European Bronchiectasis Registry (EMBARC)	Felix Ringshausen/James Chalmers	ERS 2019 Madrid	Healthcare Professionals
Abstract	**Risk factors for new P. aeruginosa Isolation in bronchiectasis- data from the European Bronchiectasis Registry (EMBARC)**	Pierre Regis Burgel/James Chalmers	ERS 2019 Madrid	Healthcare Professionals
Publication	Bronchiectasis in India: results from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) and Respiratory Research Network of India Registry	James Chalmers	Lancet Global Health August 2019	Healthcare professionals
Publication	The European Multicentre Bronchiectasis Audit and Research Collaboration (**EMBARC**) ERS Clinical Research Collaboration.	James Chalmers	ERS November 2018	Healthcare professionals
Publication	Cross-infection risk in patients with bronchiectasis: a position statement from the European Bronchiectasis Network (**EMBARC**), **EMBARC**/ELF patient advisory group and European Reference Network (ERN-Lung) Bronchiectasis Network.	James Chalmers	ERS January 2018	Healthcare professionals
Abstract	Sputum metabolites correlate with neutrophilic inflammation in bronchiectasis	Ashley Giam/James Chalmers	Bronchiectais and NTM workshop, Vienna July 2019	Healthcare Professionals

Nature of Communication	Title	Responsible Participant (and presenter when relevant)	Date/location when relevant.	Target audience
Abstract	Differences in the burden of disease and management practices for bronchiectasis across 5 EU countries: data from the EMBARC registry	James Chalmers	Bronchiectais and NTM workshop, Vienna July 2019	Healthcare professionals
Oral presentation	Inflammation in bronchiectasis	James Chalmers	ATS conference 2019, May Dallas Texas USA	Healthcare professionals
Abstract	Characteristics of patients with pulmonary non-tuberculous Mycobacterial infection in bronchiectasis: Data from the EMBARC registry	M. Loebinger	ERS conference, Paris 2018	Healthcare professionals
Abstract	Rhinosinusitis is associated with increased symptoms and more frequent exacerbations among patients with bronchiectasis- data from the EMBARC registry	M. Shteinberg (Haifa, Israel)	ERS conference, Paris 2018	Healthcare Professionals
Abstract	Comparison of bronchiectasis cohorts from tertiary centres in Sydney, Milan and Dundee reveal differences in severity and patterns of care	S. Vissier (Sydney, Australia)	ERS conference, Paris 2018	Healthcare professionals
Abstract	Validity of COPD diagnosis in Bronchiectasis patients: data from the EMBARC registry	M. Pinto Mendes	ERS conference, Paris 2018	Healthcare professionals
Abstract	Primary ciliary dyskinesia in adults with bronchiectasis: Data from the Embarc registry		ERS conference, Paris 2018	Healthcare professionals
Abstract	Sex differences in bronchiectasis patient characteristics: an analysis of the EMBARC cohort S. Finch (Perth, United Kingdom)	A. Shoemark (Dundee (Angus), United Kingdom)	ERS conference, Paris 2018	Healthcare Professionals
Abstract	The heterogeneity of bronchiectasis patient characteristics,	J. Chalmers (Dundee (Angus), United Kingdom)	ERS conference, Paris 2018	Healthcare professionals

	management and outcomes across Europe: Data from the EMBARC registry			
Nature of Communication	**Title**	**Responsible Participant (and presenter when relevant)**	**Date/location when relevant.**	**Target audience**
Abstract	Impact of Inflammatory bowel disease in bronchiectasis (IBD-BR) data from the EMBARC registry	A. De Soyza (Newcastle-upon-Tyne, United Kingdom)	ERS conference, Paris 2018	Healthcare professionals
Abstract	Determinants of quality of life in bronchiectasis using the quality of life bronchiectasis (QOL-B) questionnaire: data from the EMBARC registry	E. Polverino (Barcelona, Spain)	ERS conference, Paris 2018	Healthcare professionals
Abstract	Variability in access and referral to pulmonary rehabilitation in European bronchiectasis patients enrolled in the EMBARC registry	P. Walker (Wirral (Merseyside), United Kingdom)	ERS conference, Paris 2018	Healthcare professionals
Abstract	Aspergillus sensitisation and exacerbations of bronchiectasis: data from the EMBARC registry	Rita Boaventura (Porto)	World bronchiectasis conference 2018 (Washington DC)	Healthcare professional
Oral presentation	PK and PD of Murepavadin (POL7080) in neutropenic lung infection models when evaluated by aerosol administration	Francesca Bernardini	European Cystic Fibrosis Society Conference 2019, Liverpool (UK)	CFF community
Oral presentation	Outer-membrane targeting antibiotics: from discovery to the clinic	Daniel Obrecht	ASM microbe, San Francisco, June 23rd	Healthcare
Poster presentation	Activity of Murepavadin Against Colistin-resistant Pseudomonas aeruginosa Clinical Isolates	Francesca Bernardini	ECCMID, April 13-16, 2019, Amsterdam, The Netherlands	Healthcare
Oral presentation	Infection and Inflammation in bronchiectasis	James Chalmers	World bronchiectasis conference 2018 (Washington DC)	Healthcare professional
Oral Presentation	Bronchiectasis and primary ciliary dyskinesia	James Chalmers	Patient support group, Milton Keynes, UK	Patients

Nature of Communication	Title	Responsible Participant (and presenter when relevant)	Date/location when relevant.	Target audience
Workshop	Bronchiectasis and NTM infections	James Chalmers	Food and Drug Administration, Washington DC USA- 8th April 2019	Regulators
Oral Presentation	Bronchiectasis State of the Art and update from the European Bronchiectasis Registry	James Chalmers	Airway Vista and 1st Asian Bronchiectasis Registry Meeting, Seoul South Korea	Healthcare Professionals
Oral presentation	Patient involvement in clinical research	James Chalmers	Scottish bronchiectasis patient support group, Edinburgh March 2019	Patients
Oral Presentation	Infection in bronchiectasis	James Chalmers	ERS lung science conference, Estoril, March 2019	Healthcare professionals
Oral presentation	Bronchiectasis registries	James Chalmers	Rare lung disease conference, Milan, Italy 2019	Healthcare profesisonals
Oral presentation	State of the art management of bronchiectasis	James Chalmers	North Portugal respiratory conference, Porto February 2019	Healthcare profesionals
Workshop	Overlap between bronchiectasis and airways disease	James Chalmers, Stuart Elborn, Others	ERS seminar/workshop, Barcelona, February 2019	Healthcare professionals
Oral presentation	Post-TB bronchiectasis- data from the EMBARC registry	James Chalmers	Liverpool school of tropical medicine seminar December 2018	Healthcare professionals
Oral presentation	Update from the EMBARC registry	James Chalmers	NYU bronchiectasis symposium, New York USA, December 2018	Healthcare professionals
Oral presentation	Cough and sputum- diagnosis of bronchiectasis	James Chalmers	Primary care respiratory conference, Telford UK, September 2018	Primary care clinicians and allied healthcare professionals
Presentation to government	Bronchiectasis	James Chalmers	Meeting of the cross party committee on lung health of the Scottish Parliament	Politicians and the general public

Nature of Communication	Title	Responsible Participant (and presenter when relevant)	Date/location when relevant.	Target audience
Oral presentation	Bronchiectasis in India	James Chalmers	Meeting of the Indian bronchiectasis registry steering committee, Delhi, India, September 2018	Healthcare professionals

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
- The results from WP6 susceptibility testing of isolates in the iBEST-1 study will be published in peer-reviewed journals.
- Comparison of novel (LCI, CT and microbiome) and conventional endpoints will be published in peer-reviewed journals, likely in multiple publications in years 4-6 of the project.
- Further results from WP7 susceptibility testing will be published in peer-reviewed journals
- Analysis of Whole Genome Sequencing of CF & BE data will be published in peer-reviewed journals likely in multiple publications in years 3-6 of the project.
- POL7080 Biofilm results have being published in peer-reviewed journals.
- βENaC animal model results will be published in peer-reviewed journals, over the course of the project.

4 Management of Project and Consortium

4.1 Overall management of the project

The management of the project continued in the same vein as period 3 with strong collaboration among the consortium. The year began with the announcement of another change in the project DoW and the Management Board engaged fully with the process of finding suitable replacement partners and programmes of work which fitted with the overall aims of the project.

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.

Representatives from the management board attended a mid-project review with IMI and a panel of external experts. The consortium appreciated the review and feedback from all involved and have as a result made a

number of changes in the new version of the DoW recently approved by IMI. The use of the information in the WP5 registry in particular has been addressed in a new WP11. The consortium have also looked at how information is disseminated and our work is publicised and have placed considerably more focus in this area. The team also plan to look at further patient engagement in the coming year.

The annual General Assembly in 2019 will again European Respiratory Society congress which will be held in Madrid in September. At this year's meeting we plan to review each work package and the progress made this year. We will also introduce the new partners and programmes of work and discuss proposed work plans for Years 5 and 6.

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.

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

All comments and recommendations highlighted in the P3 report have been noted by the consortium and addressed where necessary.

4.3 Project plan for the remaining reporting periods

Period 5 will follow the project plan outlined in Description of Work v3.4 (assuming this is approved by IMI)

WP1 will focus on implementing the new Description of Work, including new work packages 9, 10 and 11

WP4 will close following the publication of the iBEST1 clinical trial results in Q4 2019

WP5 The focus now is on rapid dissemination of the extensive data that is now available from the registry. Recruitment will continue although the management board agrees that there is unlikely to be substantial additional scientific value to recruiting 20000 patients when data is already available on 16000 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.

WP6 In line with the completion of the iBEST trial in WP4, WP6 will complete the following tasks in Q4 2019

- completion of microbiome analysis (NGS, qPCR) 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 endpoint and CT parameters.
- Completion of the paper describing the image analysis of all available iBEST CTs.
- AA-ratio image analysis will be completed 18 months after last patient last visit date. Currently the automatic analysis algorithm is in development. Manual annotations are the golden standard for this method and are currently ongoing.

- Analysis of sputum inflammatory biomarker data collected in iBEST-1 study and comparison with conventional and other exploratory endpoints.
- Publication of results in peer-reviewed journals.

WP6 will then close and activities will be consolidated into the new WP11

WP7 Will continue to support the pre-clinical preparation of POL7080

- Pre-clinical toxicology of the inhaled formulation will be finalized in rodents and non-human primates. Q4 2019
- An additional inhaled-study with pigs is being performed by Polyphor to evaluate PK/PD.
- The definitive formulation and inhalation device will be selected for the clinical studies. Q4 2019
- CMC preparation for the clinical trial, including production, filling, labelling.
- The animal model of CF and the biofilm model will be developed further.
- Analysis of the Whole Genome Sequencing data will be performed.
- The development of a liposomal formulation is being explored.
- The period for analysis and publication of the scientific output, and for development of scientific tools (biofilm and animal models) will be extended to last until the end of iABC, in order to maximize utilization of the collected data and to take the development as far as possible.

WP8 The procurement process to engage a CRO to manage the clinical trial will be completed early in Q4 2019. Various activities around preparation of the study are ongoing at Polyphor.

The Phase Ia study, PK and safety study in healthy subjects and Phase1b PK, safety and Proof of Concept (POC) study in CF patients will be carried out.

WP9 Phase I parts III-2, III-3, part IVa and part IVb clinical trials will be carried out and preparation will begin for Phase II study with ALX-009

WP10 Phase II QBW251 study will begin Q1 2020

WP11 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

Del. No.	Deliverable name	WP No.	Nature	Delivery date
D4.2	Phase II trial of TIP in BE patients (abbreviated report of outcomes)	4	R	M56
D5.4	Annual data reports.	5	R	M13, M25, M37, M49, M60, M77
D5.5	Peer reviewed publications and abstracts.	5	R	M13, M25, M37, M49, M60, M77
D6.4	NGS microbiome analysis of samples collected in Phase II TIP dose finding study and comparison of	6	R	M56

Del. No.	Deliverable name	WP No.	Nature	Delivery date
D6.9	Interim analysis (Phase II TIP dose finding study) of the responsiveness of LCI endpoint in comparison to conventional FEV_1 endpoint and CT parameters.	6	R	M56
D7.10	Full report on pre-clinical development of POL7080 solution formulation as inhalation therapy, including results of inhalation toxicology.	7	R	M60
D7.11	Report on development of a liposomal formulation for inhalation	7	R	M59
D8.1	Regulatory approval for Phase I study on POL7080 in healthy subjects. Submission of final trial protocol to IMI.	8	R	M56
D9.1a	Submission of study approvals package for Phase I ALX-009	9	R	M50
D9.1b	Confirmation of completion of site selection for ALX-009 Phase I	9	R	M50
D9.2	Phase I Clinical Study Report	9	R	M60
D9.3a	Phase I Microbiome analysis report (QUB)	9	R	M60
D9.3b	Submission of the study approvals package for Phase II ALX-009 study	9	R	M60
D10.2	First Patient first visit in Phase II trial of QBW251	10	O	M59

Milestone No.	Milestone name	WPs involved	Expected delivery date	Means of verification
M6.7a	Results of LCI Healthy volunteer study	6	M52	Report
M6.8	BE Scoring baseline CTs	**6**	M57	Abstracts at scientific conferences and journal article
M7.10	Pre-clinical inhalation toxicology of POL7080 solution formulation completed.	7	M54	D7.10
M7.11	Development of POL7080 completed to enable decision on whether to proceed to clinical trials.	7	M54	D7.10
M7.12	Development of a Liposomal Formulation for inhalation completion	7	M54	D7.11
M9.2	Last patient Last visit in Phase I study	9	M56	Notification
M9.3	Safety and tolerability determined in healthy volunteers, CF and NCFBE patients	9	M57	Interim Safety Report (blind)
M9.4	Regulatory submission of phase IIa study in CF patients	9	M59	Receivability form/document
M11.2	Transfer of registry samples from UNIVDUN to QUB	6	M52	Material transfer agreement

4.4 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.

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	VH	H	Mitigation plans to be drawn up as soon as situation becomes clear	QUB	Situation to be monitored	Nov 2019
WP7 Specific toxicity demonstrated of inhaled formulation in animal models	L	MH	Use of resources for alternative antibacterial compound (if timelines allow it)	QUB	Situation to be monitored	Ongoing
WP7 Clinical development halted, for instance due to results in trials with IV-formulation	M	VH	Use of resources for alternative antibacterial compound (if timelines allow it)	QUB	Situation to be monitored	Ongoing
WP7 Delay of preclinical toxicology due to CRO capacity	VH	H	Lost time will have to partially be made up in the clinical trial phase.	UMCU / POL	Situation to be monitored	Ongoing
M6.7 CT website development	M	L	The website is currently active and after a pilot study test will be operational for the upcoming WP11 study. We have a maintenance contract that allows us to deal with hard and software upgrades, security issues and unforeseen errors when the website is used in a clinical study. When needed, novel functionalities can be programmed when an additional budget is available. . will be used for studies in WP11.	Prof H Tiddens	Website to be monitored	Q4 2020

VH = Very High, H = High, M = Medium, L = Low

5 Finance – Cost

5.1 Cost summary

- **Reporting of costs incurred by IMI beneficiaries and third parties**

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