Periodic project report

Inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis

iABC

Grant Agreement No 115721

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Period 08/2015 – 07/2016

Reporting Period 1

Description of work - 24 August 2015/DoW_0.5v

Date of submission – 1st November 2016

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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.4 of Annex 2 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:

□ has achieved most of its objectives and technical goals for the period with relatively minor deviations;

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

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 Annex 2 of the Grant Agreement.

Name of the Coordinator : ..... Manh Jorel.

Date: 31/OCT/2016

Signature of the Coordinator: .....

1. November 2016

ACHIM KAUFHOLD

1. Executive summary

1.1 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 20 partners in 7 countries, 2 pharmaceutical EFPIA member companies, Novartis and Basilea 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 contains activities to deliver the objectives outlined below

- To develop an inhaled formulation and dispersion device for BAL30072, a novel antibiotic with activity against a broad range of MDR Gram-negative pathogens (34, 35)
- To determine the pharmacokinetics and safety of BAL30072 in CF and BE patients and to provide some initial efficacy data
- To determine the therapeutic efficacy of Tobramycin inhaled powder (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

1.2 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
- WP2 supports the pre-clinical development of BAL30072. Development includes assessment of in-vitro activity, biofilm activity and in-vivo efficacy in a CF-mouse model. WP2 also contains formulations and inhalation devices development and pre-clinical safety, in line with requirements of health authorities to proceed to clinical studies.
- WP3 supports the clinical development of BAL30072 for use in CF patients; it also contains a Phase Ia study in healthy volunteers to determine the maximum tolerated dose and to assess safety and pharmacology, and a Phase Ib study in CF patients to determine a tolerable dose and generate safety, pharmacology and first efficacy data.
- WP4 supports the clinical development of two inhaled antibacterial agents for patients with BE, BAL30072 and TIP:

(i) WP4A contains a Phase 1b study of BAL30072 in BE patients to determine a tolerable dose and generate safety, pharmacology and first efficacy data.
(ii) In WP4B, 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.

1.3 Summary of progress versus plan since last period

This is the first periodic report of the iABC consortium and the team have made significant progress against the planned milestones in this first year. Some difficulty was encountered due to a protracted procurement process for the CRO required for WP4B. This resulted in the re-planning of the Novartis sponsored Phase II trial and a subsequent DoW amendment request in terms of both timescales and budget. Significant effort on the part of the consortium team however has ensured that this work package is now on track.

The second more significant issue encountered during this period was in work package 2. Patent safety concerns and programmatic issues have resulted in the withdrawal of BAL30072 from the project. This will have implications for the DoW relating to work packages 2, 3, 4A and 6. At the time of report submission, the consortium is evaluating mitigation possibilities and is actively seeking new EFPIA partners to replace the work intended for BAL30072.

1.4 Significant achievements since last report

One of the major achievements of this period is the extent to which the consortium has positively engaged in terms of partnership and the plan of work. Other key achievements include:-

- Establishment of the consortium governance strategy
- Establishment of independent review boards (Ethic Board and Data Monitoring Committee)
- Launch of the project website and newsletter communications.
- A communication strategy to define the direction of the project communication, messages, target groups, tools and organization of both internal and external communication has been developed.
- A Collection of 1018 CF (and BE)-pathogens, more than half of which have been collected during the project, and susceptibility testing of these micro-organisms against 9 antibiotics (including BAL30072) has been completed. Dissemination will occur in the form of a scientific publication, to be drafted in the coming year.
- Proof of concept technical feasibility of using existing lyophilized BAL30072 vials to prepare BAL30072, for pulmonary administration using marketed nebulized devices.
- The FDA and EMA have approved the revised study design of the Novartis sponsored TIP studies. The regulatory authorities recognised that the revised study design will identify the most appropriate dose, dose frequency (once versus twice daily dosing) and regimen (continuous versus month on / month off dosing) in patients with Bronchiectasis. Furthermore, the revised study endpoints and longer study duration will provide a better

indication of the impact of inhaled tobramycin on clinical as well as microbiological endpoints.

- The procurement of all vendors for the Novartis Phase-II study iBEST-1 has been completed, awarding 5 clinical vendors/subcontractors contracts. The main CRO, ICON plc was contracted by the managing entity (Queen's University Belfast) and study sponsor (Novartis) through competitive tendering. Other vendors were directly contracted by Novartis. Furthermore, governance was established for sample logistic and data transfer with partners and vendors.
- A highly professional data co-ordinating centre has been established at the University of Dundee to support the EMBARC European Bronchiectasis Registry. The EMBARC team support site enrolment, 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.
- An LCI Training programme, eLearning tool and a central LCI reading service have been established at Queen's University Belfast.
- Standard project protocols have been developed for DNA extraction, PCR, NGS and CT scanning.
- A central laboratory microbiology manual has been developed for use in the Phase II iBEST-1 study. This manual includes details of quantitative culture for *P. aeruginosa,* detection of other potential pathogens (*Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Staphylococcus aureus*) and antimicrobial susceptibility testing of tobramycin and comparator antibiotics.

2. Summary of progress against objectives

2.1 Summary table

Work - Package Number	Milestone/ Deliverable	Date Due (Annex I- description of work)	Completed (Yes/Not yet/Partially)	Dissemin. level[1]	Related document attached (Yes/No/Not applicable)
1	M1.1/D1.1 Signature of the Project Agreement	M1	Yes	PU	Not applicable
1	M1.2/D1.2 Kick off meeting	M3	Yes	PU	
1	M1.3 Appoint members of the governance bodies	M3	Yes	PU	
1	D1.3 Publication of a Communication Plan	M6	Yes	PU	
1	M1.4 Establishment of a project platform	M9	Yes	PU	
2	M2.1: Preliminary report on technical feasibility of Developing BAL30072 as an inhalation therapeutic. Decision on whether to proceed to actual development and to inhalation toxicology and inhalation DMPK.	M8	Yes. Further development halted	CO	Yes (as in D2.1)
2	M2.2: Development of nebulized formulation with adequate device for BAL30072.	M12	Partially. Further development halted	CO	Yes
2	M2.5 *In vitro* microbiological testing of BAL30072 activity against CF	M12	Partially	CO	Not applicable.report will follow in M15 (D2.5)

[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.

	pathogens completed.				
Work - Package Number	**Milestone/ Deliverable**	**Date Due (Annex I- description of work)**	**Completed (Yes/Not yet/Partially)**	**Dissemin. level[2]**	**Related document attached (Yes/No/Not applicable)**
2	D2.1 Preliminary report on technical feasibility of delivering BAL30072 as inhalation therapy by DPI.	M8	Yes	CO	Yes
2	D2.2 BAL30072 as a nebulized formulation with suitable device.	M12	Partially. Further development halted	CO	Yes
2	D2.6 BAL30072 biofilm testing results.	M18: M12, in DoW, is an error	No, M12 is an error (D2.6 reports on M2.6, due in M15)	NA	Not applicable,
4B	M4.1 Formation of trial steering committees.	M3	Yes: TSC* in place for phase II bronchiectasis study (Kick-off held in Sep 2015)	CO	Not applicable,
4B	M4.2 Regulatory feedback for Phase II trial of TIP in BE patients.	M3	Yes (June 2015)	CO (Feedback from authorities shared with TSC)	No (confidential)
4B	M4.3 Site selection and pre-identification complete for phase II TIP study.	M6	Partially: Pre-selection done by TSC Dec 2015. CRO site selection currently ongoing due to delays in CRO start (due by Oct 2016)	TSC	No (confidential)
4B	M4.4 First patient first visit in Phase II trial of TIP.	M9 (initial DoW) Amendment M15	As per amendment, on track for M15	Management Board	Not applicable
4B	D4.1 Regulatory advice for Phase II trial of TIP in BE patients	M4	Yes	Feedback form authorities shared with TSC	No (confidential)
5	M5.1 Regulatory and ethical	M7	yes		Not applicable,

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	approvals and registry start				
Work - Package Number	**Milestone/ Deliverable**	**Date Due (Annex I- description of work)**	**Completed (Yes/Not yet/Partially)**	**Dissemin. level[3]**	**Related document attached (Yes/No/Not applicable)**
5	Completion of electronic CRF	M6	Yes		Not applicable
5	D5.1: Alignment of proposed registry fields with international registries	M6	Yes		Not applicable
5	D5.3 First patient enrolled into the registry	M7	Yes		Not applicable,
5	M5.2/ D5.6 Publication of research Roadmap	M13	yes		Yes
5	M5.3 Enrolment of first 1000 patients	M14	yes		Not applicable
5	D5.5 First Manuscript submission/publication	M13	yes		Yes
5	M5.4 Active participation of 20 EU countries	M14	yes		Not applicable
6	M6.3: Purchase of Ecomedics Exhalyzer D devices for Multiple breath washout (MBW) testing and training and qualification in Lung Clearance index (LCI) measurement in 25 centres in preparation for WP4B BE study.	M7	Partially 25 devices purchased.		Not applicable
6	D6.7: Selected sites involved in LCI measurement for BE Phase II study set up and trained		Partially 5/25 devices installed at 5 sites. Remaining 20 sites to be decided through independent (CRO)		Not applicable

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			site feasibility assessment. Training programme and eLearning tool developed. www.MBWtraining.com 5 sites with devices trained.		
Work - Package Number	**Milestone/ Deliverable**	**Date Due (Annex I- description of work)**	**Completed (Yes/Not yet/Partially)**	**Dissemin. level[5]**	**Related document attached (Yes/No/Not applicable)**
6	M6.4: Set-up of a central LCI reading service in QUB.	M7	Yes Protocols, guidelines and email address (lcioverreading@qub.ac.uk) for central reading service set up and functional.		Not applicable
6	D6.8: Central LCI reading service (QUB) set up and functional	M7	Yes Protocols, guidelines and email address (lcioverreading@qub.ac.uk) for central reading service set up and functional.		Not applicable
6	M6.7: Website for standardization of chest computed tomographies (CTs) in Phase II study.	M6	Partially Protocols and SOPs for CT scanning are finalized. Website concept finished and tested in PDF format. Developers are currently building framework.		Not applicable
6	M6.3: Purchase of Ecomedics Exhalyzer	M7	Partially		Not applicable

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	D devices for MBW testing and training and qualification in LCI measurement in 25 centres in preparation for WP4B BE study.		25 devices purchased.		
Work - Package Number	**Milestone/ Deliverable**	**Date Due (Annex I- description of work)**	**Completed (Yes/Not yet/Partially)**	**Dissemin. level[6]**	**Related document attached (Yes/No/Not applicable)**
6	D6.7: Selected sites involved in LCI measurement for BE Phase II study set up and trained		Partially 5/25 devices installed at 5 sites. Remaining 20 sites to be decided through independent (CRO) site feasibility assessment. Training programme and eLearning tool developed. www.MBWtraining.com 5 sites with devices trained.		Not applicable
6	M6.4: Set-up of a central LCI reading service in QUB.	M7	Yes Protocols, guidelines and email address (lcioverreading@qub.ac.uk) for central reading service set up and functional.		Not applicable
6	D6.8: Central LCI reading service (QUB) set up and functional	M7	Yes Protocols, guidelines and email address (lcioverreading@qub.ac.uk) for central reading service set		Not applicable

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			up and functional.		
Work - Package Number	**Milestone/ Deliverable**	**Date Due (Annex I- description of work)**	**Completed (Yes/Not yet/Partially)**	**Dissemin. level[7]**	**Related document attached (Yes/No/Not applicable)**
6	M6.7: Website for standardization of chest CTs in Phase II study.	M6	Partially Protocols and SOPs for CT scanning are finalized. Website concept finished and tested in PDF format. Developers are currently building framework.		Not applicable

Work also completed in this period

Work Package 2

The progress of the tasks without foreseen milestones or deliverables in Work Package 2 (biofilm model development and testing, whole genome sequencing and analysis, preclinical toxicology and breakpoint development) over the first year reporting period has been as follows:

Biofilm:

Fifty P. aeruginosa isolates have been selected for biofilm testing. The Calgary biofilm method is currently being used to determine PD parameters such as the BIC (biofilm inhibitory concentration) of tobramycin, colistin and aztreonam. Due to the withdrawal of Basilea's IMP, BAL30072 will not be used in the biofilm assays. Nevertheless, these procedures are ready to be used with other potential compounds. A procedure to perform and analyze results with the BIOFLUX open model has been developed with tobramycin, and will be used after testing using the Calgary biofilm method is completed.

Whole Genome Sequencing and analysis:

Whole genome sequencing (WGS) commenced in March 2016 with the collected strains. Automation of DNA purification has been explored and included both MagnaPure (Roche) and QiaCube (Qiagen) vs manual methods. Automation of DNA purification explored to achieve results comparable with manual methods. For the majority of the species DNA purification and sequencing procedures have been verified, including for mucoid isolates. DNA validation sets have been generated for *Acinetobacter baumannii, Escherichia coli, Enterobacter cloacae complex, Enterococcus faecium, Klebsiella oxytoca, Klebsiella pneumonia, Pseudomonas aeruginosa, Serratia marcescens,* and *Stenotrophomonas maltophilia*. Currently, the validations of SeqSphere with these sets are being prepared and core genomes for the different species are being established.

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Animal model:

Following discussions with WP2 colleagues the work plan and standard-operating-procedures (SOPs) for the pre-clinical evaluation of BAL30072 were developed and agreed. Following the withdrawal of BAL30072, the intention is to proceed with the comparison of preclinical P. aeruginosa infection models to evaluate the efficacy of aerosolised antibiotics using tobramycin. If an alternative IP is brought into the iABC-program its preclinical assessment can rapidly be carried out in the most clinically relevant models identified.

Toxicology:

Based on discussions between the partners an appropriate pre-clinical toxicological testing program was developed, and the local authority permitted the animal experiments. Due to the withdrawal of Basilea's IMP this program has been discontinued before animal testing was initiated. Whether further toxicological work will be pursued in this WP will depend on whether an alternative IMP is brought into the iABC-program for which (pulmonary) toxicological testing is required.

Work Package 4B

Regulatory advice for Phase II trial of TIP in BE patients (M4.2 & D4.1) were received from both EMA and US FDA prior to protocol finalization. The final protocol was reviewed and finalized by steering committee. CRO procurement was successfully conducted for Phase II trial of TIP in BE patients. The Ethic Commitee has reviewed and provided input to the Informed Consent Form.

Work Package 6

Sputum microbiology and susceptibility testing:

Academic partners at Antwerp and QUB have been working closely with Novartis to develop a central laboratory microbiology manual to be used in the Phase II TIP study. This manual will include details of quantitative culture for P. aeruginosa, detection of other potential pathogens (including *Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Staphylococcus aureus*) and antimicrobial susceptibility testing of tobramycin and comparator antibiotics.

Molecular analyses as exploratory endpoints to measure changes in composition of the airway microbiome and resistome**:**
QUB have purchased and setup an Illumina Miseq which will be used for next-generation sequencing (NGS). Standardized protocols have also been developed for DNA extraction, PCR and NGS. Initial experiments have been undertaken to compare qPCR vs. quantitative culture for P. aeruginosa in pure culture and in sputum from patients with CF.

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

Work Package 2

M2.2 and D2.2: Development of nebulized formulation with adequate device for BAL30072**.**

Preliminary testing was undertaken for different solutions of BAL30072 with three different nebulizers. Several combinations of BAL30072 solutions and nebulizers appeared adequate in the tests in terms of pH, osmolarity and particle size distribution. However, a definitive combination of a BAL30072-formulation and nebulizer was not selected at this point due to the cessation of work following the withdrawal of Basilea IMP. The report on the development of the nebulized

formulation describing activities completed up to this timepoint is enclosed. The report describes the completed proof-of-concept work which shows that the reconstituted solution from BAL30072 lyophilized vials could be nebulized using marketed devices although additional testing according to the Requirements for Pharmaceutical Development of Inhalation Products (EMEA/CHMP/QWP/49313/2005) would be required to confirm the acceptability of a nebulized formulation and device for clinical use.

M2.5 In vitro microbiological testing of BAL30072 activity against CF pathogens completed
Milestone 2.5 comprises 3 elements of the description of work: 2.2.1, 2.2.3 and 2.2.4

2.2.1 MICs of BAL30072 and 5 comparator antibiotics determined for 1000 selected CF-pathogens obtained from UMCU, QUB and SERMAS-HURYC. This part has been fully completed. In fact 1018 strains were tested for susceptibility to BAL30072 and 8 comparators: ceftazidime, meropenem, imipenem, aztreonam, ciprofloxacin, tobramycin, colistin and co-trimoxazole. Report on this testing will follow in M15, as scheduled in the DoW.

2.2.3 MICs with antimicrobial peptides (e.g. LL-37, human ß-defensin 1), lung surfactant and artificial sputum medium performed on 50 isolates, and 2.2.4 Resistance induction tested on 50 selected CF isolates. Due to the withdrawal of Basilea IMP, the testing of a subset of strains for MIC with additives has been halted, as has been the resistance induction testing. This activity may be continued if a new EFPIA partner/IMP can be identified/joins the project.

See also section 1.3 of this document (deviations from the Description of Work).

Work Package 4B

M4.3 and M4.4

The Contract Research Organisation (CRO) has been selected in compliance with the public tender process under supervision of the managing entity. Due to the complexity of subcontracted services, the procurement process (tender and contracting) for the CRO was completed with delay.

The delay in the start-up activities contracted with the CRO, are translated in the revised milestones as proposed in the amendment (FPFV initially planned for M9, is currently foreseen for M15). Phase II bronchiectasis study (iBEST-1 study) is projected to complete in M33 instead of M24 in the original plan.

Timelines for the initiation and execution of the phase III trials will be impacted. Taking into account all CRO study close out activity, completion of the program is foreseen M71.

More detailed information is found in the amendment to the DoW recently submitted to IMI-JU.

Work package 6

M6.3: Purchase of Ecomedics Exhalyzer D devices for MBW testing and training and qualification in LCI measurement in 25 centres in preparation for WP4B BE study.

LCI machines (n=25) have been purchased with 5 distributed to partner sites. Due to delays in procurement of a CRO, the Phase II study (Study 4b) is now projected to complete in M33 instead of M24 as in the original plan. Due to this delay, additional clinical sites have not yet been selected. Therefore, the decision on which additional 20 sites will receive LCI equipment will be made following completion of the ICON feasibility assessment. Post decision, delivery, installation, training and certification will be performed.

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. Therefore, the website developers elected to develop the website themselves. Furthermore, during this process, extra functions were added, for which a supplementary contract was made. The concept is developed and tested in PDF format; currently programmers are programming the site. We expect the website to be ready before the start of the Phase II TIP study. It is important to note that the CTs collected in this Phase II study will be mostly made retrospectively using a wide variety of techniques. Therefore, the aim is to have the website functional for those patients that require CT after the study has been started in a centre. This will enable testing of the website and the acquired CTs. Hence, even if the website is not operational at the start of the Phase II study, it will not lead to any problems as the centre can follow their routine CT protocol. However, the website has to be fully operational prior to the start of any Phase III TIP study.

2.2 Deviations from Description of Work

Work Package 2

BAL30072 IMP has been withdrawn from the iABC project by EFPIA-partner Basilea. Therefore toxicological testing, additional formulation development and in-vivo / in-vitro testing specifically of BAL30072 has been halted. A new work plan will have to be drafted, after negotiation between the iABC partners, and with IMI. Similar activities may be continued if a new EFPIA partner/IMP can be identified/joins the project.

Work Package 4B

The phase II bronchiectasis study (iBEST-1) design has been revised following feedback from the regulatory authorities in Europe (EMA Scientific Advice received on 25 Jun 2015) and the USA (FDA type-C meeting on 23 Jun 2015). The following considerations have resulted in a study design, with an increased number of patients, an increase in visits and an increase in treatment duration.

There is a significant ongoing controversy in the field emerging from initial studies in cystic fibrosis with tobramycin and subsequently with other inhaled antibiotics licensed for use on a month on / month off basis. The Trial Steering Committee for work package 4B redesigned the phase II study to compare continuous inhaled Tobramycin (TIP) against a month on / month off regimen with an appropriate placebo and controls. This required an increase in the number of patients from 144 to 180 and extra visits. This re-designed phase II study has been found acceptable by the health authorities. The study will also make a significant contribution to defining the optimal treatment regimen with inhaled antibiotics in patients with bronchiectasis. Furthermore, this study will inform the design of future studies of inhaled antibiotics in patients with cystic fibrosis.

Following the recommendation of the expert panel at Stage 2, the consortium agreed to include measurements of inflammatory biomarkers as exploratory endpoints. These additional measurements (airways and serum) will further support building a robust package of evidence on the effect of inhaled tobramycin in patients with bronchiectasis, but were not originally budgeted.

The health authorities (FDA and EMA) support the revised study design as it will identify the most appropriate dose, dose frequency (once versus twice daily dosing) and regimen (continuous versus month on / month off dosing) in patients with bronchiectasis. Furthermore, the regulatory authorities acknowledged that the revised study endpoints and longer study duration will provide a

better indication of the impact of inhaled tobramycin on clinical as well as microbiological endpoints. The authorities also requested additional exit interviews to further evaluate the utility of the QOL-B questionnaire, in anticipation of its use in the phase III trials of inhaled tobramycin in this patient population.

This design will answer some key questions in the field of bronchiectasis treatment, better inform a phase III design and satisfy health authority requirements.

The costs for the restructured study are approximately €4m greater than initially anticipated. The Managing Entity has assessed the likely impact of the increase in costs and has predicted that cash flow will not be impacted over the first 3 years of the iABC project. The longer term financial implications will be discussed with IMI JU in light of the results of the phase II study.

On completion of the phase II study, the consortium shall take action to re-design the phase III programme (work package 4B, phase III randomised, double blind, placebo controlled study to evaluate the efficacy, safety and tolerability of TIP in patients with bronchiectasis) and examine the options for funding at that time. The consortium shall notify the IMI JU of the proposed phase III programme, including budget and deliverables, once this has been completed and agreed by the consortium. No activity related to phase-III programme in either work package 4B or work package 6 will be initiated without securing appropriate funding and agreement by all relevant parties.

3. Summary of Major Achievements and key dissemination activities

3.1 Major achievements

Work package 1

- Establishment of the consortium governance strategy
- Establishment of independent review boards (Ethic Board and Data Monitoring Committee)
- Launch of the project website and newsletter communications.
- Communication strategy and action plan. A communication strategy to define the direction of the project communication, messages, target groups, tools and organization of both internal and external communication was developed and submitted to IMI.
- DoW update. Interactions with the FDA and EMA have led to revisions of the Phase-II study iBEST-1 study design (as described in the section 2.1). Timelines for the initiation and execution of the phase II trial as well as budget are impacted. The changes have been discussed with IMI (3 Dec 2015) and a proposed update to the DoW has been drafted following will be shortly submitted.
-

Work package 2

- Collection of 1018 CF (and BE)-pathogens, more than half of which have been collected during the project, and susceptibility testing of these micro-organisms against 9 antibiotics (including BAL30072). Dissemination will occur in the form of a scientific publication, to be drafted in the coming year.

- Proof of concept technical feasibility of using existing lyophilized BAL30072 vials to prepare BAL30072, for pulmonary administration using marketed nebulized devices. However,

Basilea IMP BAL30072 has been withdrawn from the project and further development of this substance as a drug for human use is unlikely. Therefore dissemination of these findings as scientific publications will be difficult, and patents will not be pursued. Relevant results will therefore be uploaded to the ND4BB Translocation database.

Work Package 4

- Interaction with Regulatory Authorities
  The FDA and EMA interactions were prepared in collaboration with Trial Steering Committee. Prof Elborn was present for face-to-face meeting with FDA representing the consortium together with Novartis. The FDA and EMA support the revised study design as it will identify the most appropriate dose, dose frequency (once versus twice daily dosing) and regimen (continuous versus month on / month off dosing) in patients with BE. Furthermore, the regulatory authorities acknowledged that the revised study endpoints and longer study duration will provide a better indication of the impact of inhaled tobramycin on clinical as well as microbiological endpoints.
- The results of the revised phase II study will inform the design and the sample size estimates of the phase III studies. Furthermore, this study will inform the design of future studies of inhaled antibiotics in patients with cystic fibrosis.
- Contracting of all vendors for Phase-II study iBEST-1
  The procurement of all vendors has been completed awarding the 5 clinical vendors/subcontractors for Phase-II study iBEST-1. The main CRO, ICON plc was contracted by the managing entity (Belfast) and study sponsor (Novartis) through competitive tendering and successfully on-boarded by the Trial Steering Committee. Other vendors were directly contracted by Novartis. Furthermore, governance across Work-package 4B and 6 was established for sample logistic and data transfer with partners and vendors.
- The Data Monitoring Committee was established and provided feedback to the TSC on the DMC charter for the iBEST-1 study.

Work Package 5

- WP5 has established a data co-ordinating centre at the University of Dundee to support that EMBARC European Bronchiectasis Registry. 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.

Work Package 6

- Development of LCI Training programme, eLearning tool (www.MBWtraining.com) and a central LCI reading service in QUB.

- Development of standardized protocols for DNA extraction, PCR and NGS.
- Development of protocols and SOPs for CT scanning.
- Development of a central laboratory microbiology manual for use in the Phase II iBEST-1 study. This manual includes details of quantitative culture for *P. aeruginosa,* detection of other potential pathogens (*Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Staphylococcus aureus*) and antimicrobial susceptibility testing of tobramycin and comparator antibiotics.

3.2 Key dissemination activities

Nature of Communication	Title	Responsible Participant	Date	Target audience
Oral presentation at the congress of the European Respiratory Society (ERS), Amsterdam	Inhaled antibiotic therapies in Bronchiectasis	Prof Stuart Elborn (Belfast, UK)	September 28, 2015	Scientific community
ERS symposium 2015 in Amsterdam		Dr James Chalmers (Dundee, UK)	Sep 2015	Scientific community
Study information posted on Clinical trials.gov	NCT02712983	Gerhild Angyalosi (Novartis, CH)	February 5, 2016	Scientific & medical community
1st World Bronchiectasis Conference, Hannover, Germany	Project presentation	Dr James Chalmers	July 2016	Medical community, patients, policymakers

3.3 Use and dissemination of foreground

Not applicable in this period

4. Management of Project and Consortium

4.1. Overall management of the project

During this first period of the project, engagement between partners has been extremely positive. The governance structure which was outlined in the Description of Work has been implemented in full and is working effectively. There is a high degree of participation in all the committees and the decision making process is relatively smooth at this stage. Each of the work packages benefits from strong leadership and regular communication and this is evidenced in the deliverables realised.

An external Ethical Advisory Board has been established and has met once during this period. Similarly an external Data Monitoring Committee has been formed to oversee the Phase II TIP trial and this has met once.

At a coordination unit level there is interaction between the consortium and the wider ND4BB project with members providing input to the steering committee and sharing progress reports. At a management board level there are good working relationships with EMBARC, COMBACTE, ENABLE, and TRANSLOCATION

There are also good working relationships in place between the coordination unit and ECFS, ERS with the project being introduced at the ERS congress in Amsterdam in Sept 2015 and again at the ECFS conference at Basel in June 2016.

The collaboration between the non-EFPIA participants and the EFPIA partners is also proving to be effective and input from the EFPIA organisation is currently extremely helpful as the consortium navigates the current change in direction.

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

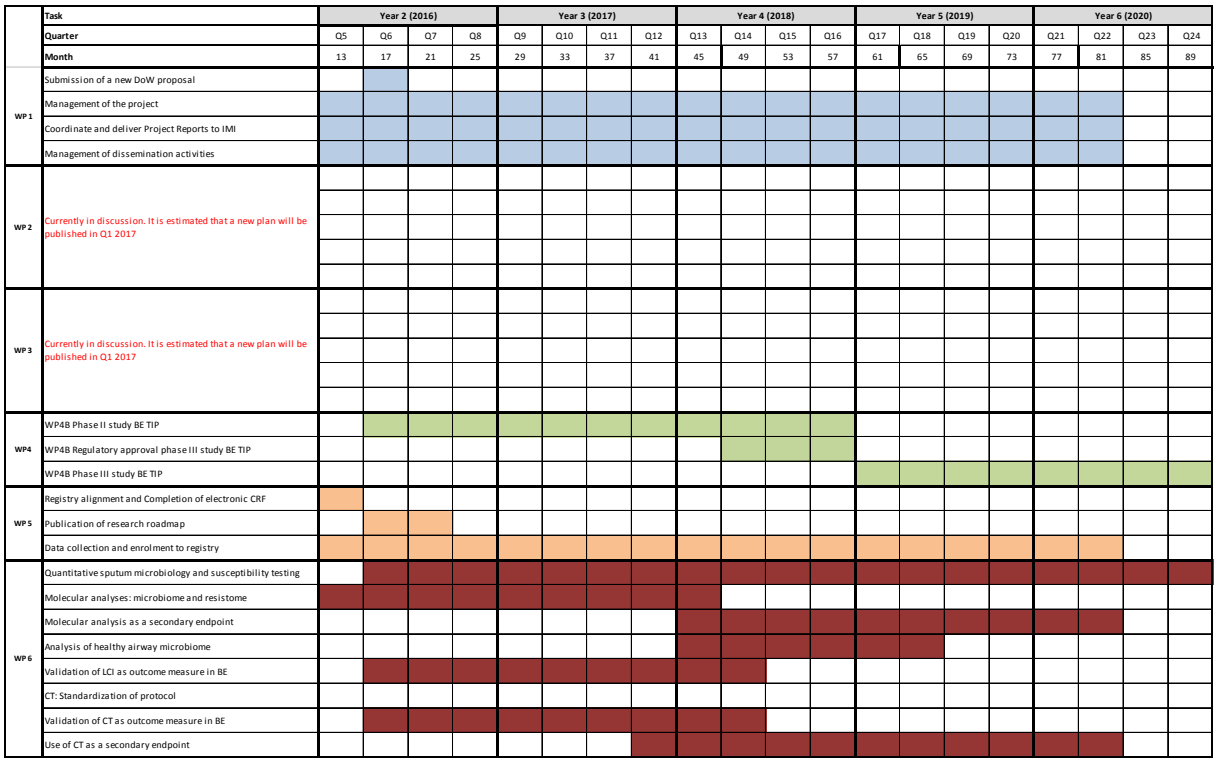
Not applicable in this period

4.3. Project plan for the remaining reporting periods

Throughout the next reporting period, the consortium will undertake a considerable body of work.

This will primarily concentrate on working to deliver a new Description of Work to achieve the outcomes on which the grant agreement was based. As these discussions continue, the work which was planned in WP2, 3 and 4A has been suspended but may resume depending on the updated plan.

The Novartis sponsored iBEST-1 Phase II trial will begin recruiting patients in October 2016 and this activity is expected to last throughout the reporting period. WP5 activity will continue as planned and WP6 activities will ramp up to support iBEST-1.



4.4. Risk assessment, when appropriate

Project Risk / Issue	Probability VH/H/M/L	Impact VH/H/M/L	Mitigation plan	Responsible Participant	Action to be taken	Due Date
WP1 Protracted discussion on project redesign causing delay	H	H	Close collaboration with IMI, EFPIA and consortium partners	All consortium partners	Weekly meetings with consortium and as required with IMI, EFPIA to resolve issues	End 2016
WP2 Change of partnership	M	M	Effective communication with affected partners to allow action plans to be put in place	All consortium partners	As per above	End 2016
WP4B iBEST-1 Study timelines	L	M	Close collaboration with CRO for sites selection and initiation	NVS/QUB/PAP/RBHT /UNIVDUN/UMIL/FC RB/UEDIN	Weekly monitoring, TSC actively engaged in new site identification.	ongoing
WP4B iBEST-1 budget	L	L		QUB/NVS	Close tracking of the CRO spending	ongoing
WP4B	H	H	Consider re-design the	QUB/NVS	On completion	M34

Phase-III study budget			phase III programme based on Phase II results		of the phase II study, the consortium shall take action to re-design the phase III programme and examine the options for funding at that time.	
WP4B Recruitment slower than expected in Phase II	L	H	Recruiting from up to 49 leading European centres with a target of 4 per site. This is based on previous studies of similar size and design (has been shown to be achievable. Recruitment from ECFS-CTN and EMBARC centres with proven record.	NVS/QUB/PAP/RBHT /UNIVDUN/UMIL/FC RB/UEDIN and ICON	Close monitoring of recruitment rates with CRO and selection of backup sites.	M25
WP5 Over-recruitment	M	M	Steps being taken to ensure the sustainability of the project and to potentially permit over recruitment	UoD	As described	M25
WP4B Imbalance in recruitment between countries	H	L	Steps being taken to moderate recruitment in the UK and enhance recruitment elsewhere	UoD	As described	M25
WP5 Loss of ERS endorseme nt	M	H	ERS endorsement expires in April 2017 and requires to be renewed. The likelihood of failing renewal is low but impact would be high	UoD	Apply October 2016 to renewed ERS endorsement	M15
M6.7 Website for standardizat ion of chest CTs not ready before start of Phase II study	L	L	We can communicate CT protocols per email when required.	Prof. H. Tiddens	Progress is closely monitored. Strategy at the service provider (program developers) can be modified.	M14

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**

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 2; Queen's University Belfast (QUB)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
1, 2, 4, 6	Personnel direct costs	*228,765.20*	*WP1 – 26.82PM – 1x academic lead, 2x project manager;* *WP2 – 12.39PM – 1x academic, 2x post doc researcher;* *WP4 – 3.76PM - 1x academic, 1x post doc researcher;* *WP6 – 1.47PM – 2x academic*
4	Subcontracting *[if foreseen in Description of Work]*	*337,972.26*	*CRO costs, subcontract review costs.*
	Other direct costs		
2,4,6	*Consumables [if applicable]*	*266,303.67*	*Misc consumables*
	Equipment depreciation [if applicable]	*0*	
1,2,4,6	*Other [if applicable]*	*31,296.68*	*€12,721.60, travel costs.* *€16,249.83 animal costs* *€770.48, computers* *€826.80, hospitality* *€727.97, NI licence training and fees*
	Indirect costs	*105,273.11*	*20% flat rate*
TOTAL COSTS		*969,610.92*	
Budget for the period		*4,700,000.00*	*Budget representative for 100% costs*
Deviation		*-3,734,923.92*	

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 4; University Medical Centre Utrecht (UMCU)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
1, 2	Personnel direct costs	*89,491*	*Personal costs including Management costs*
	Subcontracting *[if foreseen in Description of Work]*	*0*	
2	Other direct costs	*4,192*	*Costs include travel and bench fees 2015*
2	*Consumables [if applicable]*	*84,225*	*Approximately €35-40k susceptibility testing, €45-50k WGS*
	Equipment depreciation [if applicable]	*0*	
	Other [if applicable]	*0*	
	Indirect costs	*35,582*	*20% flat rate*
TOTAL COSTS		*213,490*	
Budget for the period		*160,117*	
Deviation		*53,373*	

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 5; Belfast Health & Social Care Trust (BHSCT)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
3	Personnel direct costs	*0*	
	Subcontracting *[if foreseen in Description of Work]*		
	Other direct costs		
	Consumables [if applicable]		
	Equipment depreciation [if applicable]		
	Other [if applicable]		
	Indirect costs		
TOTAL COSTS		*0*	
Budget for the period			
Deviation			

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 6; Fraunhofer-Gesellschaft (ITEM)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
2	Personnel direct costs	*12,062.94*	*Salaries of 3 scientists (1.06 PM) and 1 graduate (0.46 PM) for 1.52 PM.*
	Subcontracting *[if foreseen in Description of Work]*	*0,00*	
2	Other direct costs	*460.31*	*Traveling to Groningen (09/02/2016, iABC project meeting, 2 persons), Basel (06-07/07/2016, GA meeting, 1 person).*
	Indirect costs	*12,523.25*	*Actual indirect costs based on personnel costs.*
TOTAL COSTS		*24,619.48*	
Budget for the period			
Deviation			

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 7; University of Groeningen (RUG)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
2	Personnel direct costs	*54,876.27*	*Salary postdoc 12 pm*
2		*20,041*	*Salary technician 5.4 pm*
2		*25,667.49*	*Salary professor 2,4 pm*
2		*17,506.72*	*Salary PhD 6 pm*
	Subcontracting *[if foreseen in Description of Work]*		
	Other direct costs		
	Consumables [if applicable]		
2	*Equipment depreciation [if applicable]*	*1,811*	*Loop-5 months deprecation a 362,3 = 1811: ((Amount 19200, date invoice 29-3-2016, total deprecation months 53, this period 5)*
2	*Equipment depreciation [if applicable]*	*542*	*Dehumidifier-5 months deprecation a 108,40 = 542: ((Amount 5745, date invoice 29-3-2016, total deprecation months 53, this period 5)*
2	*Equipment depreciation [if applicable*	*6,026*	*Demo Discovery TGA-7 months deprecation a 860,8 = 6026: ((Amount 47345, date invoice 18-1-2016, total deprecation months 55, this period 7)*
2	*Equipment depreciation [if applicable*	*3,726*	*Inhaler10 months deprecation a 372,6 = 3726: ((Amount 21609, date invoice30-10-2015, total deprecation months 58, this period 10)*
2	*Other [if applicable]*	*2,592*	*Lab chemicals*
	Other	*2,493*	*Lab supplies*
	Other	*886.53*	*Travel costs Basel 6-6-2016/7-6-2016 meeting IABC*
	Indirect costs	*27,233.50*	
TOTAL COSTS		*163,401.03*	
Budget for the period		*124,795.35*	
Deviation		*38,605.78*	*More personal cost were made so far*

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 8; SERVICIO MADRILENO DE SALUD (SERMAS)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
2	Personnel direct costs	36,697.78	*11.2 PM (Hired personnel cost: María Díez (9 PM) + Own-Staff Personnel cost; R.Cantón, MI. Morosini, M.Tato (2.2 PM)*
	Subcontracting *[if foreseen in Description of Work]*		
	Other direct costs	*39,712.43*	
2	*Travel*	*429.72*	*Attendance of María Díez Aguilar to the Annual General Assembly Meeting of i-ABC. (Basilea. 7/06/16)*
2	*Consumables*	*4,207.17*	*Plates, culture media, immunoassay kits consumable for laboratory works as swabs, filters, etc.*
2	*Equipment depreciation*	*35,000*	*Bioflux System (Izasa Scientific)*
2	*Other*	*75.54*	*Samples shipment to Utrecht*
	Indirect costs	*15,282.04*	*20% flat rate*
TOTAL COSTS		*91,692.25*	
Budget for the period			
Deviation			

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 9; Antwerp University Hospital (UZA)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
6	Personnel direct costs	*92,031.97*	*Salaries of 2 junior lab personnel 10.75 PM* *2 senior lab personnel 4.8 PM* *lab director for mgt of this project 0.9 PM*
	Subcontracting *[if foreseen in Description of Work]*		
	Other direct costs		
6	*Consumables [if applicable]*	*7,512.33*	*Lab consumables*
6	*Equipment depreciation [if applicable]*	*3,086.71*	*Depreciation 5 years of -80°C freezer* *This has been calculated according to the local deprecation rules*
6	*Other [if applicable]*	*9,555*	*ICT consumables – support package*
	Indirect costs	*20,154.04*	*20% flat rate*
TOTAL COSTS		*112,186.00*	
Budget for the period			
Deviation			

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 10; University of Dundee (UNIVDUN)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
5	Personnel direct costs	*71,958.55*	*Salaries of Investigator (1.87 PM), Project Co-Ordinator (11 PM), Project Manager (3 PM), and Research Admin (1 PM)*
	Subcontracting *[if foreseen in Description of Work]*		
	Other direct costs		
5	*Consumables [if applicable]*	*2,687.34*	*Translation of registry materials, Computer equipment, printing of registry materials (consent forms, information sheets, flyers etc)*
	Equipment depreciation [if applicable]		
5	*Other [if applicable]*	*84,857.69*	*Payments to sites for registry enrolment, website maintainence and admin, investigator, steering committee and patient travel for investigator meetings*
	Indirect costs	*31,900.72*	*20% flat rate*
TOTAL COSTS		*191,404.30*	
Budget for the period			
Deviation			

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 12; Institut National de la Santé et de la Recherche Médicale (INSERM)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
3	Personnel direct costs	*0*	
	Subcontracting *[if foreseen in Description of Work]*		
	Other direct costs		
	Consumables [if applicable]		
	Equipment depreciation [if applicable]		
	Other [if applicable]		
	Indirect costs		
TOTAL COSTS		*0*	
Budget for the period			
Deviation			

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 12; Université de Poitiers (UP)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
3	Personnel direct costs	*0*	
	Subcontracting *[if foreseen in Description of Work]*		
	Other direct costs		
	Consumables [if applicable]		
	Equipment depreciation [if applicable]		
	Other [if applicable]		
	Indirect costs		
TOTAL COSTS		*0*	
Budget for the period			
Deviation			

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 12; Università degli Studi di Milano (UMIL)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
1,4	Personnel direct costs	*7,979.37*	*1 M/M effort of Prof. Francesco Blasi:* • *0.8 M/M for activities related to WP4* • *0.2 M/M for activities related to WP1*
	Subcontracting *[if foreseen in Description of Work]*		
1,4	Other direct costs	*406.31*	*Travel costs for participation to iABC meeting in Basel*
	Consumables [if applicable]		
	Equipment depreciation [if applicable]		
	Other [if applicable]		
	Indirect costs	*1,677.14*	*20% flat rate*
TOTAL COSTS		*10,062.82*	
Budget for the period		*23,431.20*	
Deviation		*-13,368.38*	*The deviation is due to PI decision to take care directly of the activities in the starting phase of the project. For next periods it is already foreseen the recruitment of junior staff (PostDocs).*

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 1201; FONDAZIONE IRCCS CA' GRANDA OSPEDALE MAGGIORE POLICLINICO (IRCCS CA' GRANDA)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
4	Personnel direct costs	*0*	
	Subcontracting *[if foreseen in Description of Work]*		
	Other direct costs		
	Indirect costs		
TOTAL COSTS		*0*	
Budget for the period			
Deviation			

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 13; Hospices Civils de Lyon (Lyon General Hospitals) (HCL)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
3	Personnel direct costs	*0*	
	Subcontracting *[if foreseen in Description of Work]*		
	Other direct costs		
	Consumables [if applicable]		
	Equipment depreciation [if applicable]		
	Other [if applicable]		
	Indirect costs		
TOTAL COSTS		*0*	
Budget for the period			
Deviation			

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 14; Medizinische Hochschule Hannover (MHH)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
4A	Personnel direct costs	*3,755.53*	*Technican (1,05 Months)*
	Subcontracting *[if foreseen in Description of Work]*		
	Other direct costs		
	Consumables [if applicable]		
	Equipment depreciation [if applicable]		
	Other [if applicable]		
	Indirect costs	*751.11*	*20% flat rate*
TOTAL COSTS		*4,506.64*	
Budget for the period		*4,444.25*	
Deviation		*62.39*	

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 15; University of Antwerp (UANTWERP)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
…	Personnel direct costs	*0*	
	Subcontracting *[if foreseen in Description of Work]*		
	Other direct costs		
	Consumables [if applicable]		
	Equipment depreciation [if applicable]		
	Other [if applicable]		
	Indirect costs		
TOTAL COSTS		*0*	
Budget for the period			
Deviation			

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 16; University of Edinburgh (UEDIN) with NHS Lothian as 3rd Party			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
4B	Personnel direct costs	*17,336.17*	*Adam Hill, PI, 1.37 PM*
	Subcontracting *[if foreseen in Description of Work]*		
	Other direct costs		
	Consumables [if applicable]		
	Equipment depreciation [if applicable]		
	Other: Travel	*99.10*	*Project work Ireland – 26th -27th April 2016 (P Fitch)*
	Indirect costs	*3,487.05*	*20% flat rate*
TOTAL COSTS		*20,922.33*	
Budget for the period			
Deviation			

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 17; Royal Brompton & Harefield NHS Foundation Trust (RBHT)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
4B	Personnel direct costs	*13,940.10*	*Salary costs for 1Scientist/Lead Investigator*
	Subcontracting *[if foreseen in Description of Work]*		
	Other direct costs		
	Consumables [if applicable]		
	Equipment depreciation [if applicable]		
	Other [if applicable]		
	Indirect costs	*2,788.02*	*20% flat rate*
TOTAL COSTS		*16,728.12*	
Budget for the period			
Deviation			

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 18; FUNDACIO CLINIC PER A LA RECERCA BIOMEDICA (FCRB)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
4B	Personnel direct costs	*8,267.47*	*Personnel costs corresponding to Eva Polverino (IP). Tasks developed in the framework of WP4 (1.95 PM).*
	Subcontracting *[if foreseen in Description of Work]*	*0.00*	
	Other direct costs	*0.00*	
	Consumables [if applicable]	*0.00*	
	Equipment depreciation [if applicable]	*0.00*	
	Other [if applicable]	*0.00*	
	Indirect costs	*1.653.49*	*20% flat rate*
TOTAL COSTS		*9,920.96*	
Budget for the period		*9,600.00*	
Deviation		*320.96*	

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 1801; Hospital Clínic i Provincial de Barcelona (HCRB)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
4B	Personnel direct costs	*0*	
	Subcontracting *[if foreseen in Description of Work]*		
	Other direct costs		
	Consumables [if applicable]		
	Equipment depreciation [if applicable]		
	Other [if applicable]		
	Indirect costs		*20% flat rate, actual indirect costs*
TOTAL COSTS		*0*	
Budget for the period			
Deviation			

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 19; Papworth Hospital NHS Foundation Trust (PAP)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
4B	Personnel direct costs	*0*	
	Subcontracting *[if foreseen in Description of Work]*		
	Other direct costs		
	Consumables [if applicable]		
	Equipment depreciation [if applicable]		
	Other [if applicable]	*356.06*	*Training costs*
	Indirect costs	*71.21*	*20% flat rate*
TOTAL COSTS		*427.27*	
Budget for the period			
Deviation			

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 20; ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM (EMC)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
6	Personnel direct costs	*19,777.37*	*PhD student (396 hrs period May 2016 – July 2016; € 11832,48) + Project manager (175.5 hrs period Aug 15 – Juli 2016; € 7944,89)*
	Subcontracting *[if foreseen in Description of Work]*		
	Other direct costs		
	Consumables [if applicable]		
	Equipment depreciation [if applicable]		*depreciation of important equipment (provide detail)*
6	*Hardware/Software/licence costs*	*14,404.06*	*Development website*
	Indirect costs	*6,836.29*	*20% flat rate*
TOTAL COSTS		*41,017.72*	
Budget for the period		*112,604.40*	
Deviation		*-71,586.68*	

Direct financial contribution

- **Reporting of costs incurred by EFPIA companies**

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 3; Novartis Pharma AG (NOV)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
1, 4B & 6	Personnel direct costs (fully loaded FTE costs)	*1,067,182.20*	*5.62 fully loaded FTEs (=67.48 PMs) engaged in:* • *WP1: Novartis representatives in iABC governance (coordination Unit, Management Board and SCOC)* • *WP4B: Co-lead and Trial management of iABC iBEST-1 Phase-2 study including preparation of all study related material (protocol and related documents), management of CRO start-up activities, regulatory activities (DRA Hub), Supply testing and management* • *WP6: Co-leader and support to all activities linked to Bronchiectasis Phase-2 study*
4B	Subcontracting *[if foreseen in Description of Work]*	*345,257.36*	*WP4B: Ongoing contracts with 4 vendors on iBEST-1 Phase-2 study*
4B	Consumables *[if foreseen in Description of Work]*	*0.0*	*Note:* *WP4B: Consumables i.e. Tobramycin Inhaled Powder clinical supply not included in this Y1 reporting. Actuals will be added as Y1 amendment at Y2 reporting*
Sub-total in kind contribution		*1,412,439.56*	
Direct financial contribution		*133,826.00*	*WP1 & WP6: QUB (Queen's University Belfast)*
Total in kind contribution		*1,546,265.56*	
Of which Non-EU in kind contribution[8]		*727,063.02*	*WP 4B: Novartis clinical and technical team members located in East Hanover (NJ, USA) and San Carlos (CA, USA)*
Budget for the period		*3,982,043.00*	*1/5 of total commitment*
Deviation		*-2,435,777.44*	*[Note: WP4B Consumables not yet included]*

[8] when there is a special clause 13 in the Grant Agreement

TABLE: PERSONNEL AND OTHER MAJOR COST ITEMS INCLUDING SUBCONTRACTING			
Participant # 1; Basilea Pharmaceutica International Ltd (Basilea)			
Work relevant to Work-Package(s)	Item description	Amount in €	Explanations of the use of resources
1, 2 & 3	Personnel direct costs (fully loaded FTE costs)	*417,853.00*	*1.71 fully loaded FTEs (=20.56 PMs) engaged in:* • *WP1: Management activities* • *WP2: Development inhalation device for BAL30072, invitro antimicrobial activities of BAL30072 against CF pathogens, ßENac-Tg mouse infection model development and in vivo efficacy of BAL30072, Pre-clinical inhalation TOX and DMPK,* • *WP3: discussions on Phase 1 studies*
2	Consumables:		• *WP 2: 100 samples shipped to Universtity Groeningen*
Sub-total in kind contribution		*441,704.00*	
Direct financial contribution (RTD contribution)		*64,770.00*	*Queen's University Belfast (three quarterly payments)*
Total in kind contribution		*506,474.00*	
Budget for the period		*1,127,962.00*	*1/5 of total commitment*
Deviation		*-621,488.00*	*IMP withdrawal*

6. Form C and Summary Financial Report

The following must be submitted as separate PDF files (originals should be sent by surface mail):

- Summary financial report, extracted from SOFIA (Submission OF Information Application)
- Form Cs for each participant (beneficiary, third party, EFPIA companies), extracted from SOFIA
- Certificate on financial statements[9]

[9] when the cumulative amount of costs claimed by participant is equal to or superior to EUR 375.000 and in any case for the final reporting period.