Inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis (iABC)

IMI 11th call: ND4BB Topic 7

Mid-project review 30th Nov 2018

Agenda

- Status of the iABC project

- WP1: Project Management and Communication
- WP2: Pre-clinical development of BAL30072 as an inhaled therapy
- WP7: Preclinical development of Murepavadin as an inhaled therapy
- WP8: Clinical development of Murepavadin for CF patients
- WP5: Development of an EU bronchiectasis registry
- WP4: Clinical development of TIP for BE patients
- WP6: Novel outcome measures for clinical trials

- Plans for 2019/2020

iABC
inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis

Project Status
November 30th 2018

Prof. Stuart Elborn
Dr David Hughes

The iABC project

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- Topic 7 of ND4BB (11th call of IMI 1)
- Coordinator: Novartis Pharma AG
- Managing entity: Queens University Belfast
- EFPIA-partners: Novartis Pharma AG and Polyphor Ltd
- 17 Academic partners:

Belfast Health and Social Care Trust
Erasmus Universitair Medisch Centrum
Vall D'Hebron - Institut De Recerca,
Hospices Civils de Lyon
INSERM
Medizinische Hochschule Hannover,
Papworth Hospital NHS Foundation Trust,
Rijksuniversiteit Groningen
Royal Brompton & Harefield NHS Trust
Servicio Madrileno De Salud, Madrid
The University Of Edinburgh
Universita Degli Studi Di Milano
Universitair Medisch Centrum Utrecht
Universitair Ziekenhuis Antwerpen,
Universiteit Antwerpen,
University Of Dundee
Queen's University Belfast

- Total budget appr. € 50 million

Unmet clinical needs

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Cystic Fibrosis

- Long term infection with Gram-negative organisms, particularly *Pseudomonas aeruginosa* (PA)
- Antimicrobial resistance to current agents

Bronchiectasis

- No licensed therapy, high unmet need
- Use of inhaled antibiotics is based on limited evidence from small pilot studies
- Morbidity and mortality driven by presence of PA

Architecture of ND4BB

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ND4BB cross topic collaboration and dissemination

Topic 1: COMBACTE
a) Enabling Clinical Collaboration
b) Clinical Development of GSK322

Topic 1c: Clinical Development of MEDI4893

Topic 2: TRANSLOCATION
Research penetration and efflux inGram-negatives. Data Hub and Learning from R & D experience

Topic 3: ENABLE
Discovery & development of new drugs combatting Gram-negative infections

Topic 4: DRIVE-AB
Driving re-investment in R&D and Responsible use of antibiotics

Topic 5 COMBACTE-CARE:
Clinical Development of antibacterial agents for Gram-negative antibiotic resistant pathogens

Topic 6: COMBACTE-MAGNET:
Systemic molecules against HAIs due to clinically challenging Gram-negative pathogens

Topic 7: iABC:
Inhaled Antibacterials in CF and non-CF BE

Dvpt-focused (Gram + infections)

Discovery-focused

Economics & stewardship

Development-focused (Gram-negative infections)

ND4BB Information Center

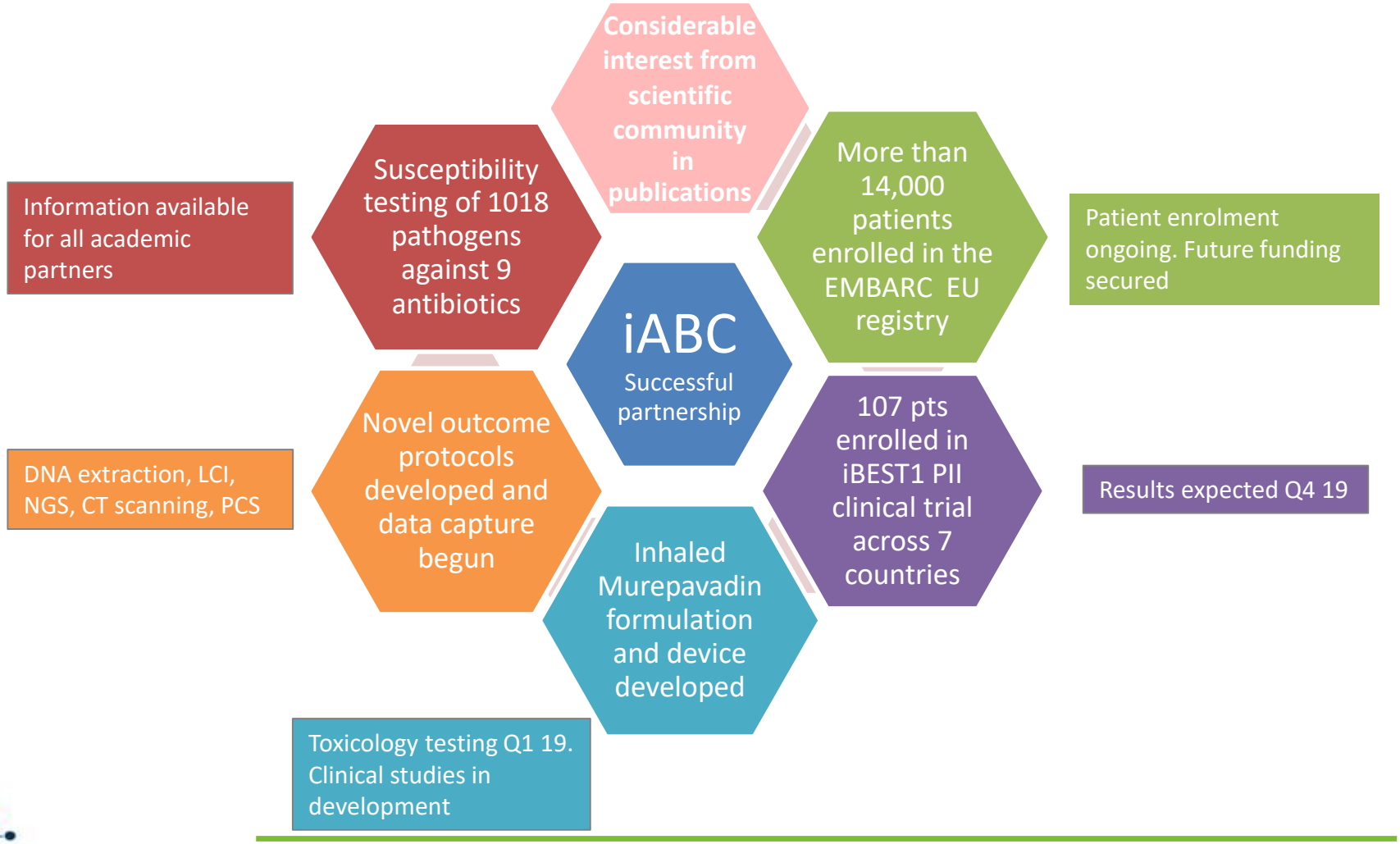
All data generated submitted and accessible to all consortium partners

Journey so far

- August 2015: iABC launched in with 18 academic and 2 EFPIA partners.
- June 2016: Basilea notified the consortium of the withdrawal of BAL30072 (WP2 &WP3A stopped)
- Sept 2017: Amendment 1 to the Grant Agreement approved by IMI

- Oct 2017: Polyphor join consortium to develop an inhaled form of its antibiotic Murepavadin (WP7 &WP8 added)
- Aug 2018: Novartis announce sale of their asset TOBI Podhaler® to Mylan (WP4 &WP6 affected)
- Oct 2018: Mitigation plan developed and call launched to find a new partner

iABC Achievements



Current challenges and risks

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- Change of consortium partnership
  - Introduction of new partner/s
  - Possibility some partners will leave
- Change in Description of Work

  2 new work packages to be added
- Time to deliver the new work plan is challenging
- Brexit

  UK relationship with EU still unclear

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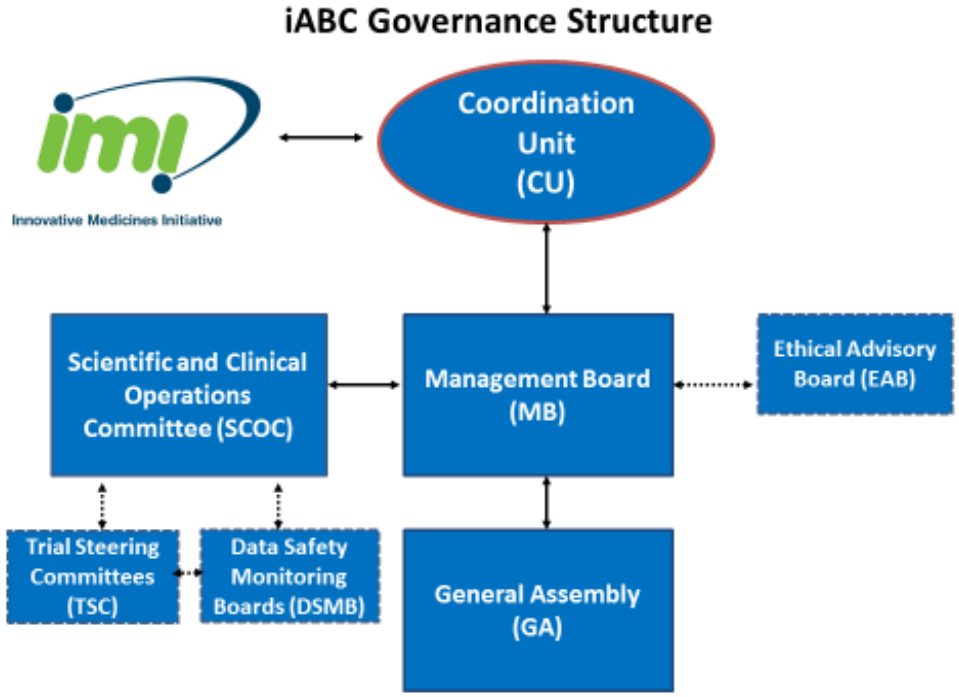
Work Package 1

Prof Stuart Elborn

Sinead Cahill

Queen's University Belfast

Governance

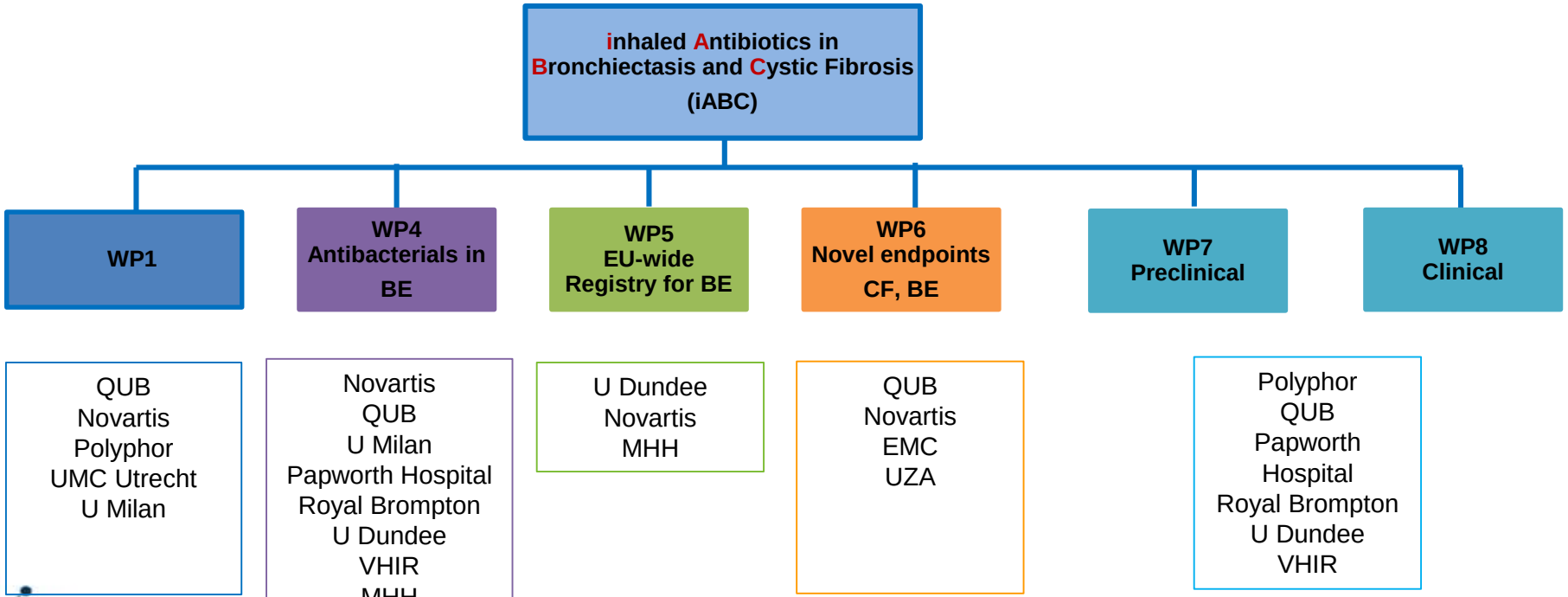


Ethical Advisory Board
Prof Scott Bell (chair) - QIMR Brisbane
Prof Harry Heijermann - UMCU
Dr Janet Allen – Cystic Fibrosis Trust
Ms Claire Hopley (patient)

Data Monitoring Committee
Prof Chris Goss (chair) – Univ Washington
Prof Laurent Nicod – Lausanne University
Prof David Mauger – Penn State

The consortium

- The collaboration between consortium members has been very positive
- Participants actively engaged
- Decision-making is by consensus
- Regular communications with all partners



Polyphor selection process

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Oct 2016

Call Launched

Promoted through EFPIA, ND4BB, Consortium forums

Nov 2016

Proposals received

3 companies submitted proposals to Managing Entity QUB

Dec/Jan 2016

Consortium review and agreement

Proposals discussed and clarified at special Management Board sessions. Agreement reached that Polyphor had the preferred proposal

Feb-April 2017

Description of Work developed

Detailed planning sessions held between Polyphor and consortium to develop new DoW

May 2017

Proposal submitted to IMI

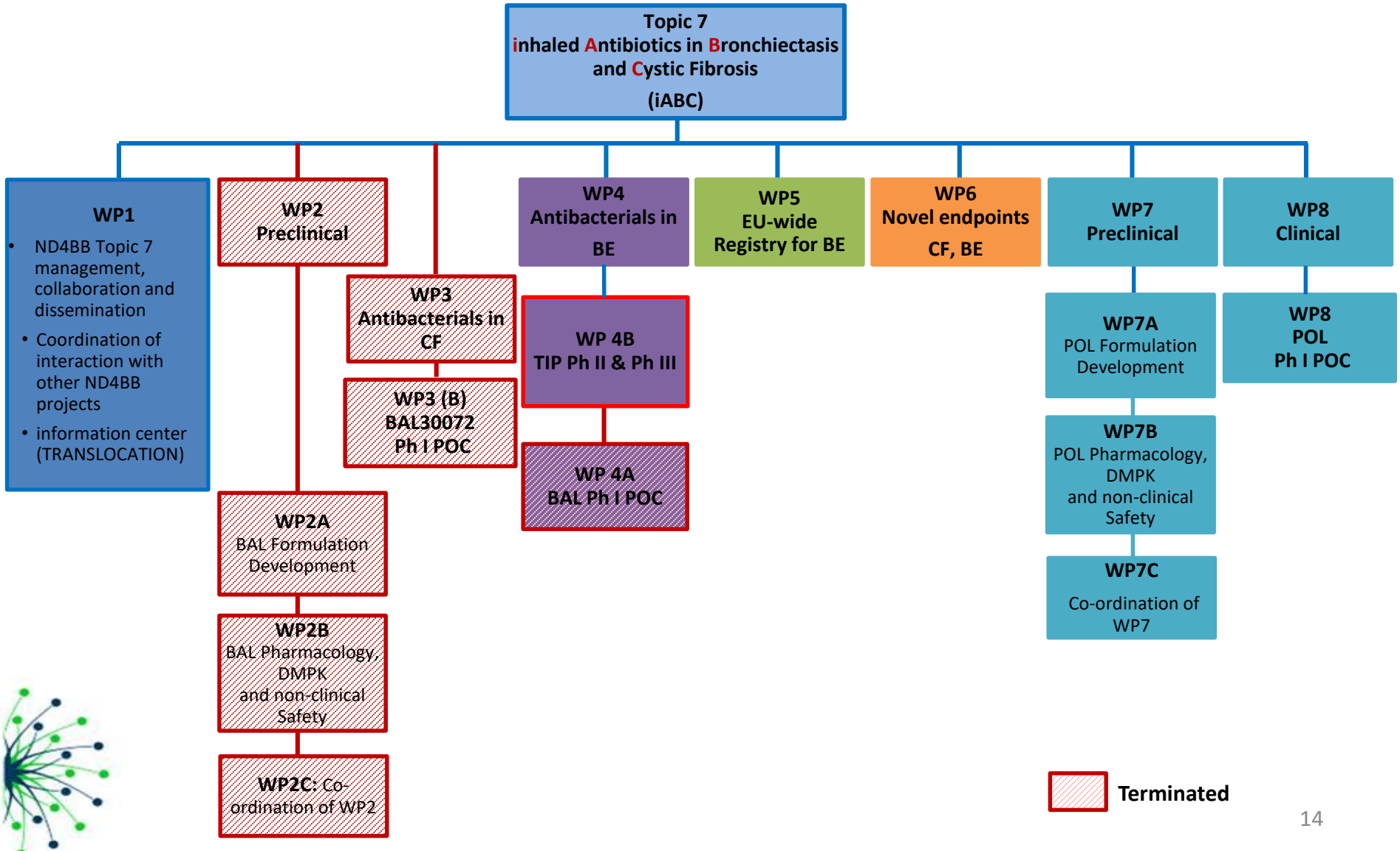
Summary of decision process and proposed description of work submitted for review

Jul – Sept 2017

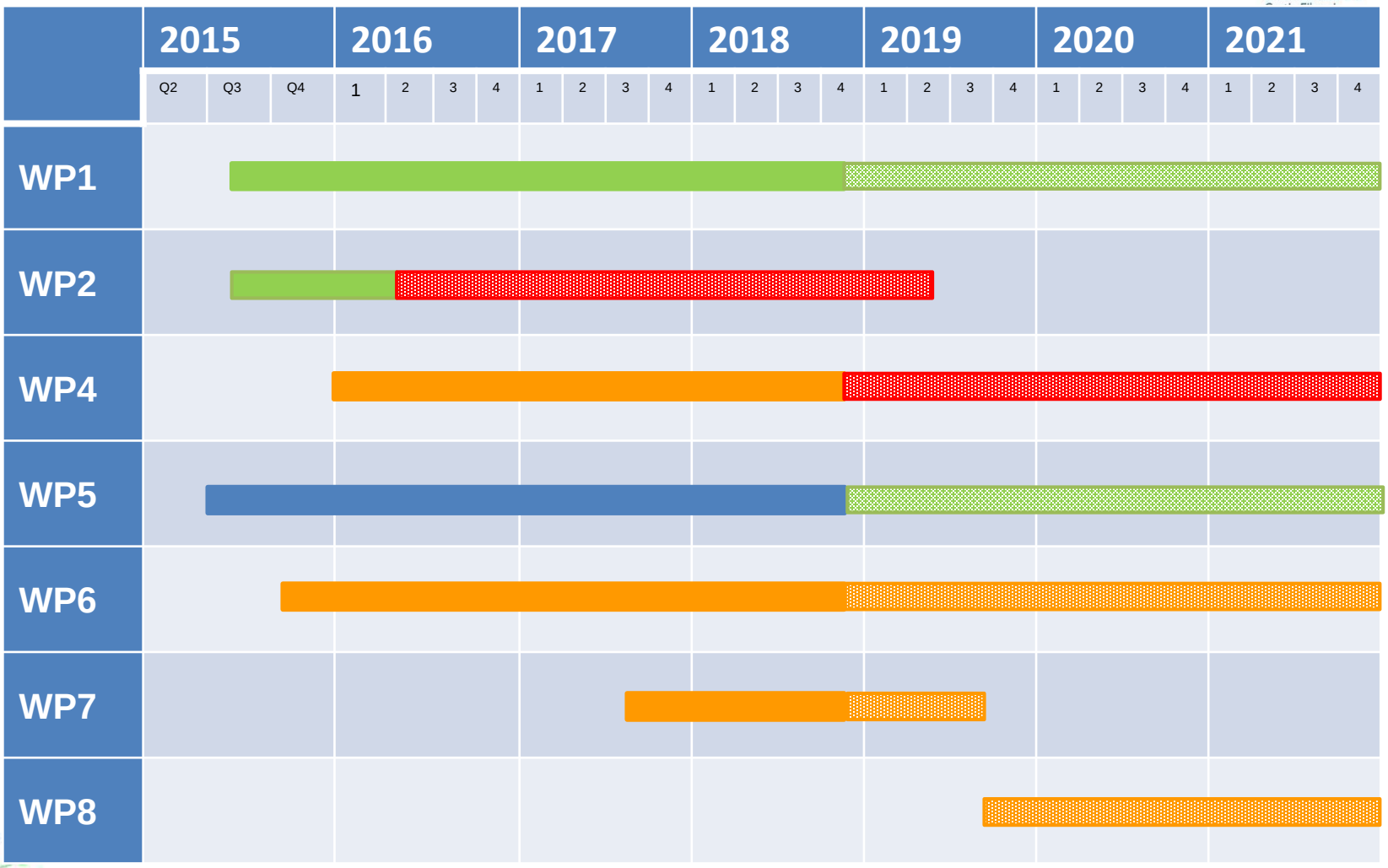
Selection process ratified and DoW amendment submitted

In July IMI approved the process of selection. Amendment submitted and approved September 2017

New Structure of iABC work packages from 2017



Project plan – Nov 2018



Ahead of plan

Tracking plan

Behind plan

Significantly behind plan/stopped

Budget

Total planned expenditure Y1-Y3

Academic Partners	EFPIA partners	Total
13.5 M€	14.2 M€	27.7 M€

Actual expenditure Y1-Y3

Academic partners	EFPIA partners	Total
8.9 M€	9.2 M€	18.1 M€

- Basilea project curtailed. Approx. 1 year to bring Polyphor on board
- Delay in WP4 Phase II clinical trial. Affected both WP4 and WP6 spend

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Budget available for new plan

Budget	Amount	IMI Funding
Original academic spend WP4 +WP6	23.2 M€	17.4 M€ (A)
Subcontract contracted spend	7.5 M€	5.6 M€ (B)
WP4 spend to date		1.98 M€ (C)
WP6 spend to date		0.45 M€ (D)

IMI Funding remaining = A – (B+C+D) = **9.37 M€**

This funding will be matched by EFPIA/BEAM partners

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Work Packages 2, 7, 8

Dr Miquel Ekkelenkamp

Dr Daniel Obrecht

Dr Stuart Elborn

Polyphor Ltd

WP 2/7: pre-clinical development

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- Development objectives
  - Establish activity in vitro (+ biofilm) and in vivo
  - Formulation and device development
  - Pre-clinical toxicology

WP2: BAL30072

WP7: murepavadin

- Scientific objectives
  - Genetic analysis of CF and BE-pathogens
  - Development of biofilm models
  - Development of beta-ENaC mouse model of CF
  - Proposal of breakpoints for inhaled therapy

Pre-clinical development BAL30072

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- Partners:
  - Basilea, UMCU, RUG, ITEM, SERMAS-HURYC, QUB
- Timelines

		2016							2017				2018				2019			
	Month	1	4	7	10	13	16	19	22	25	28	31	34	37	40	43	46	49		
WP 2	Feasibility DPI / Nebulizer BAL30072																			
	Development BAL30072 nebulizer device																			
	Development of DPI BAL30072																			
	In-vitro microbiology/ Biofilm models BAL30072																			
	In-vivo efficacy BAL 30072																			
	Mech. tox and reg. Inhalation Toxicology (rat, dog) BAL30072																			
	Manufacture clinical trial medication (several batches)																			
	Development ECOFFs and breakpoints, WGS analysis																			

- Development BAL30072 halted in Q2 2016 (toxicity issue)
  - Scientific objectives mostly continued in WP7

Formulation development BAL30072

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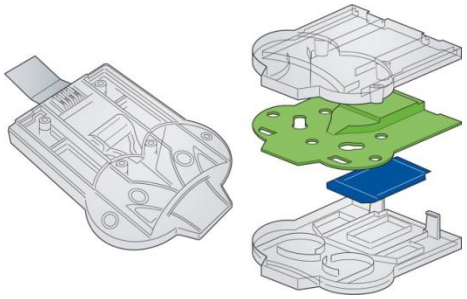
- Dry powder and nebulized formulations tested
  - Test results to lead choice which to persue
  - Both appeared feasible

Pari Velox



Twincer (DPI)

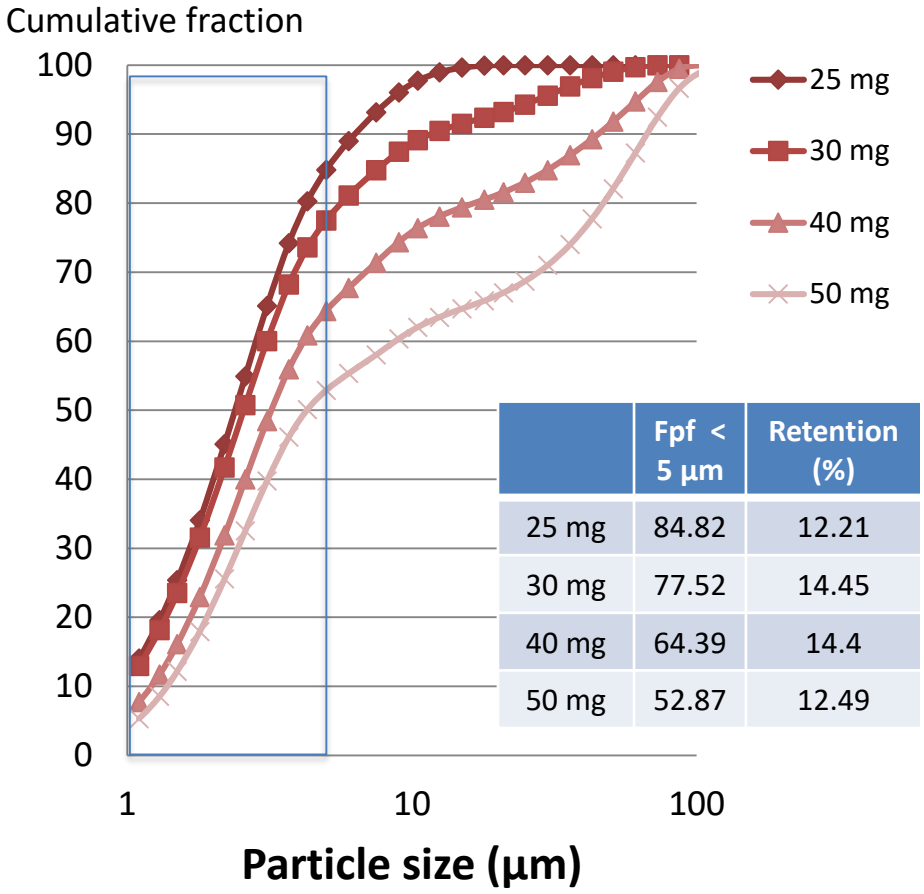
Pari eFlow

Pari LC Sprint + Turboboy

DPI development

- Conclusions:
  - Micronisation suitable method for DPI
  - Administration with Twincer feasible
  - Dispersion efficiency decreases with dose
- Work halted
  - Force control agents
  - Spray drying
  - Other inhalers

Effect dose on dispersion efficiency

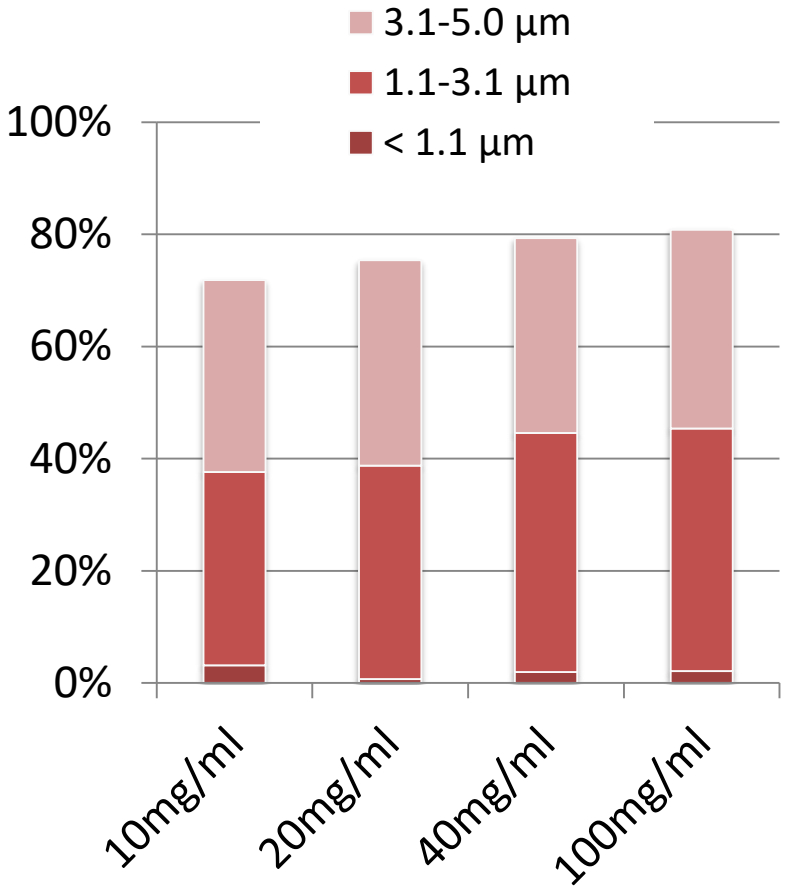


	Fpf < 5 µm	Retention (%)
25 mg	84.82	12.21
30 mg	77.52	14.45
40 mg	64.39	14.4
50 mg	52.87	12.49

Nebulization development

- Conclusions:
  - Nebulisation suitable to administer BAL30072 to respiratory tract
  - 100 mg/mL solution performed best
  - eFlow performs best considering FPF, retention and nebulisation times
  - Performance Velox just slightly less, and more patient friendly device
- Work halted:
  - Stability
  - Characterization in solution

eFlow performance by concentration



Activity of BAL30072

- 1018 Gram-negative isolates, (mostly) from CF and BE patients
  - 523 *Pseudomonas aeruginosa,* 114 *Stenotrophomonas maltophilia,* 114 *Burkholderia* spp., 103 *Achromobacter* spp., 70 *Haemophilus* spp., 63 Enterobacteriales, 19 *Ralstonia* spp., 12 *Pandoraea* spp.
- BAL30072 highly active against most species
  - In particular exceptional activity vs *Burkholderia* species
  - Limited activity against *Ralstonia* and *Pandoraea*
- Report submitted Q1 2017
- Data of 8 comparator antibiotics (vs non-*P. aeruginosa*) published
  - Díez-Aguilar e.a. Int J Antimicrob Agents 2018
  - *P. aeruginosa* data to be published w/ murepavadin + addit. comparators

P. aeruginosa

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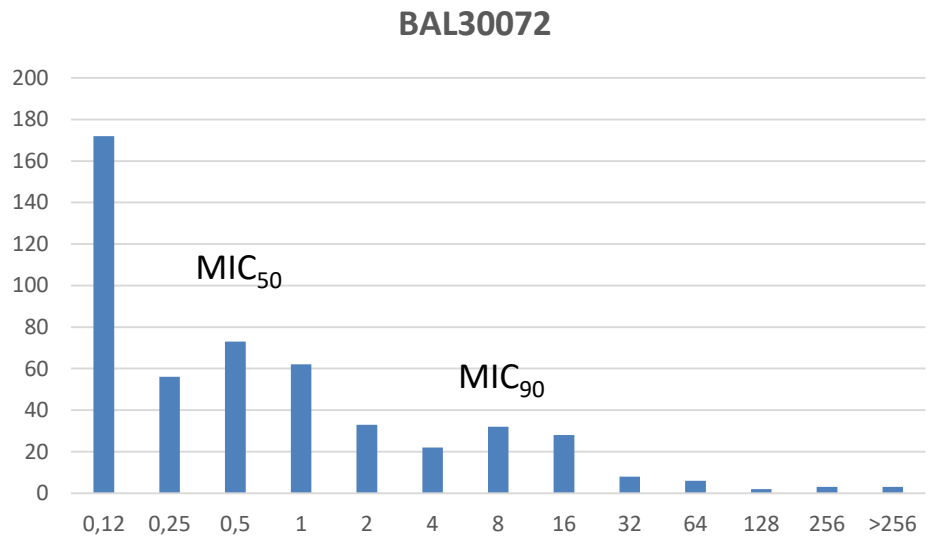

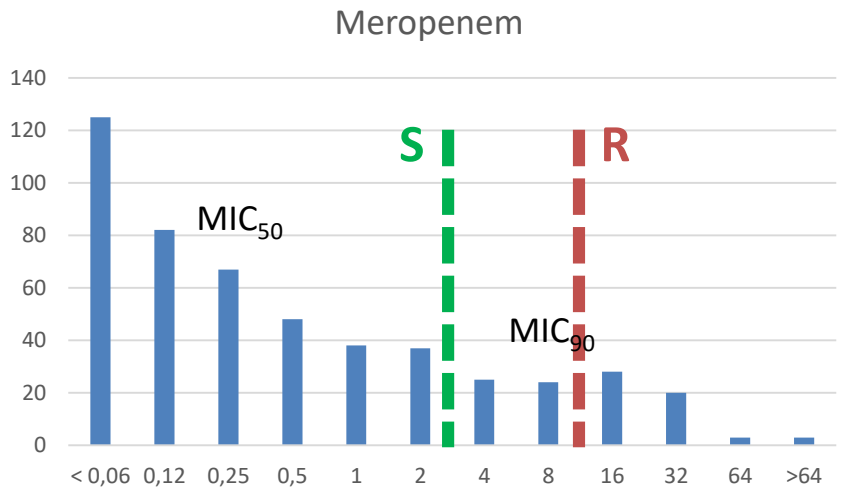

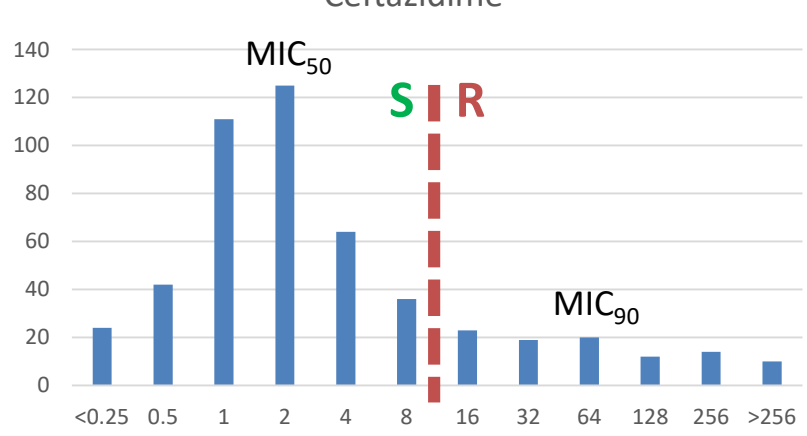

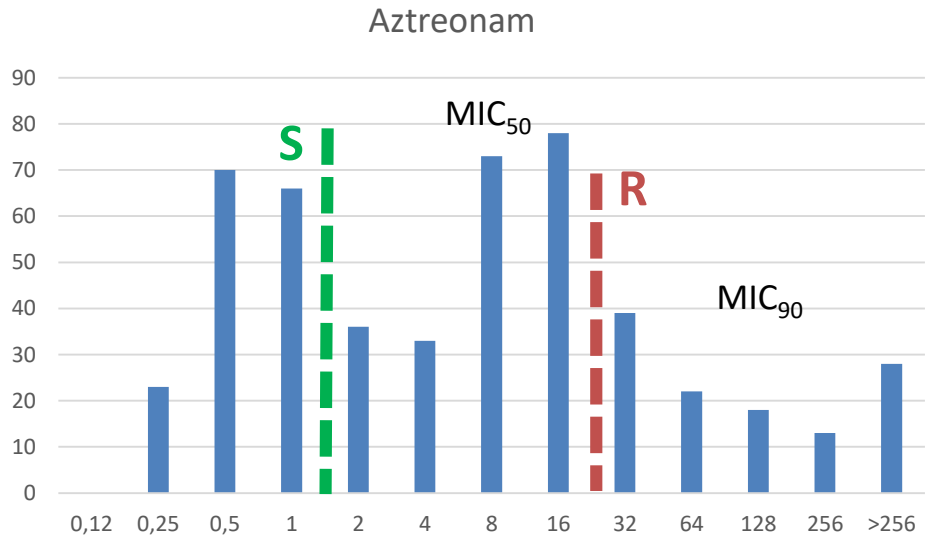

Burkholderia species

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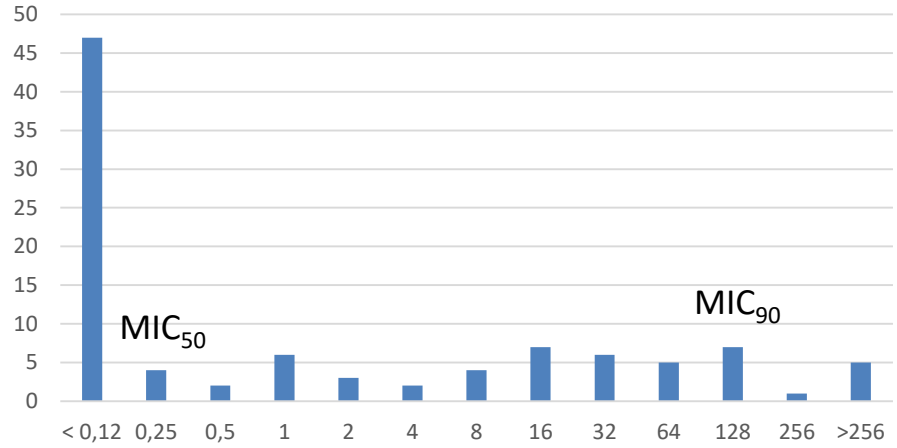
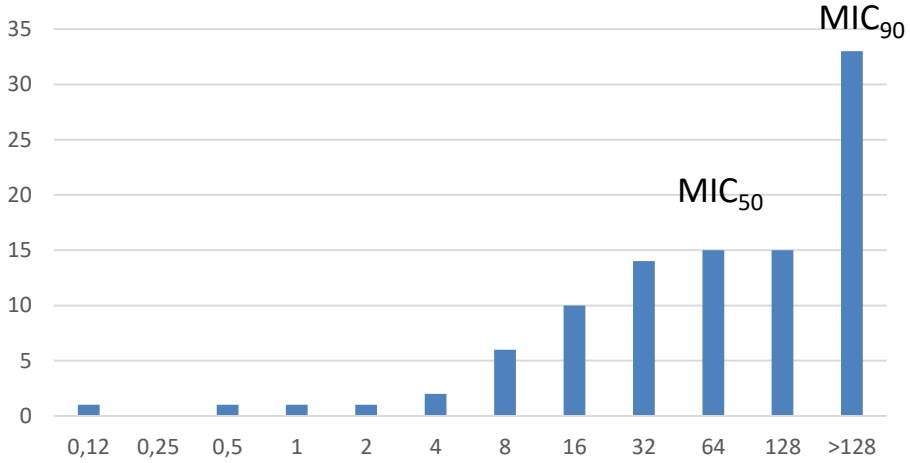
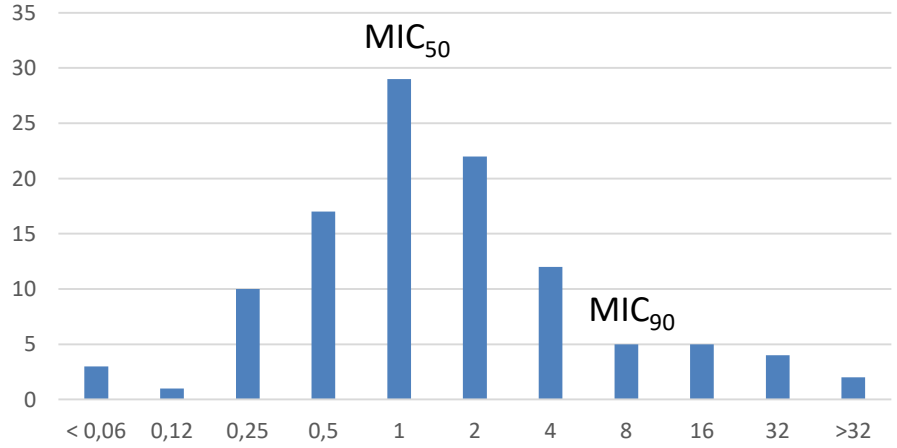
BAL30072



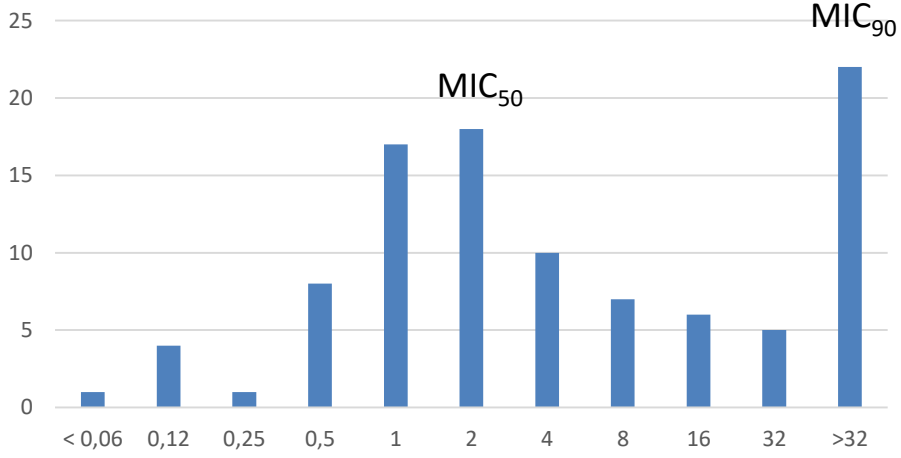
Tobramycin



Co-trimoxazole



Ciprofloxacin



Genomic analysis CF pathogens

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- Aim:
  - Sequence genome of 1000 CF/BE pathogens
  - Establish genetic relatedness and traits of CF/BE pathogens
  - Analyze resistance mechanisms in CF at genetic level
- Status:
  - >99% strains sequenced (Illumina NextSeq)
  - New alleles and sequence types currently under review

Status of sequencing

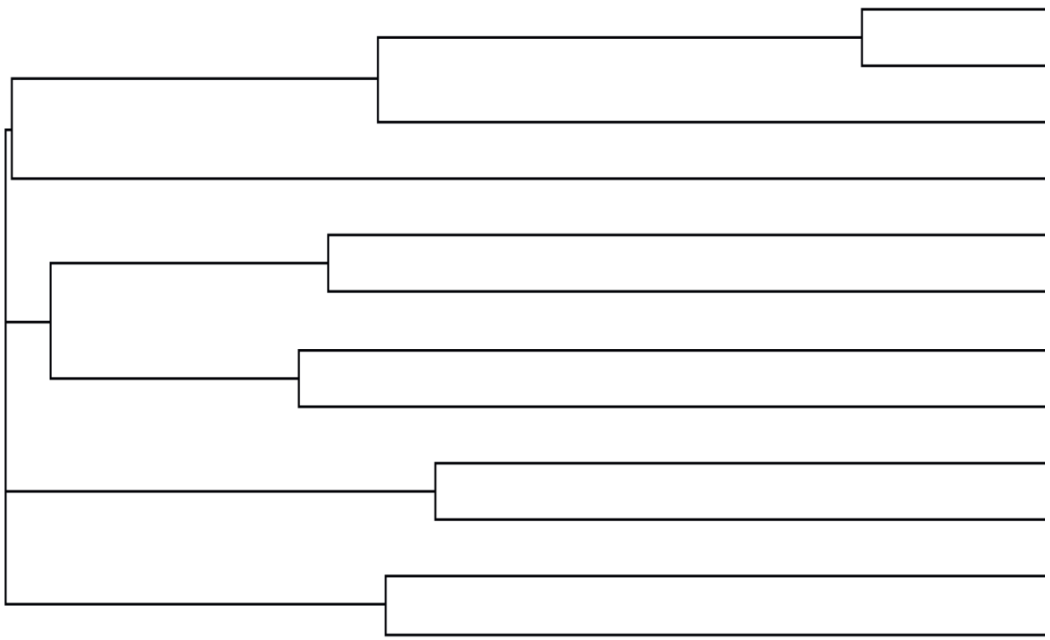
- *Achromobacter* 101/103 (2 repeatedly poor sequence)
- *Burkholderia* 105/114 (3 absent, 6 repeatedly poor sequence)
- Enterobacteriales 62/62
- *Haemophilus* 69/69
- *Pandoraea* 12/12
- *Ralstonia* 19/19
- *Pseudomonas* 521/523 (2 repeatedly poor sequence)
- *Stenotrophomonas* 111/114 (3 repeatedly poor sequence)

MLST (core genome)

	N	# STs	new ST	new alleles
Achromobacter	101	61	36?	38?
Burkholderia	105	41	>25	>19
Enterobacteriaceae	40	29	8?	3?
Haemophilus	69	52	5?	6?
Pseudomonas	488	217	26	8
Stenotrophomonas	111	54	27?	47?

remark: ? needs to be confirmed.
> the MLST scheme does not include (partial) deletions of the allele

cgMLST of Pandoraea isolates



	country	*blaOXA*
P. pulmonicola	NI	158
P. pulmonicola	NL	158
P. pulmonicola	NL	159
P. pulmonicola	SP	156
P. sputorum	NI	155
P. sputorum	SP	155
P. sputorum	SP	154
P. sputorum	SP	155
P. pnomenusa	SP	151
P. pnomenusa	NL	152
P. apista	SP	153
P. apista	SP	153

neighbor-joining tree based on allele differences among 342 genes

Taxonomic relationship of *Pandoraea* isolates with known WGS

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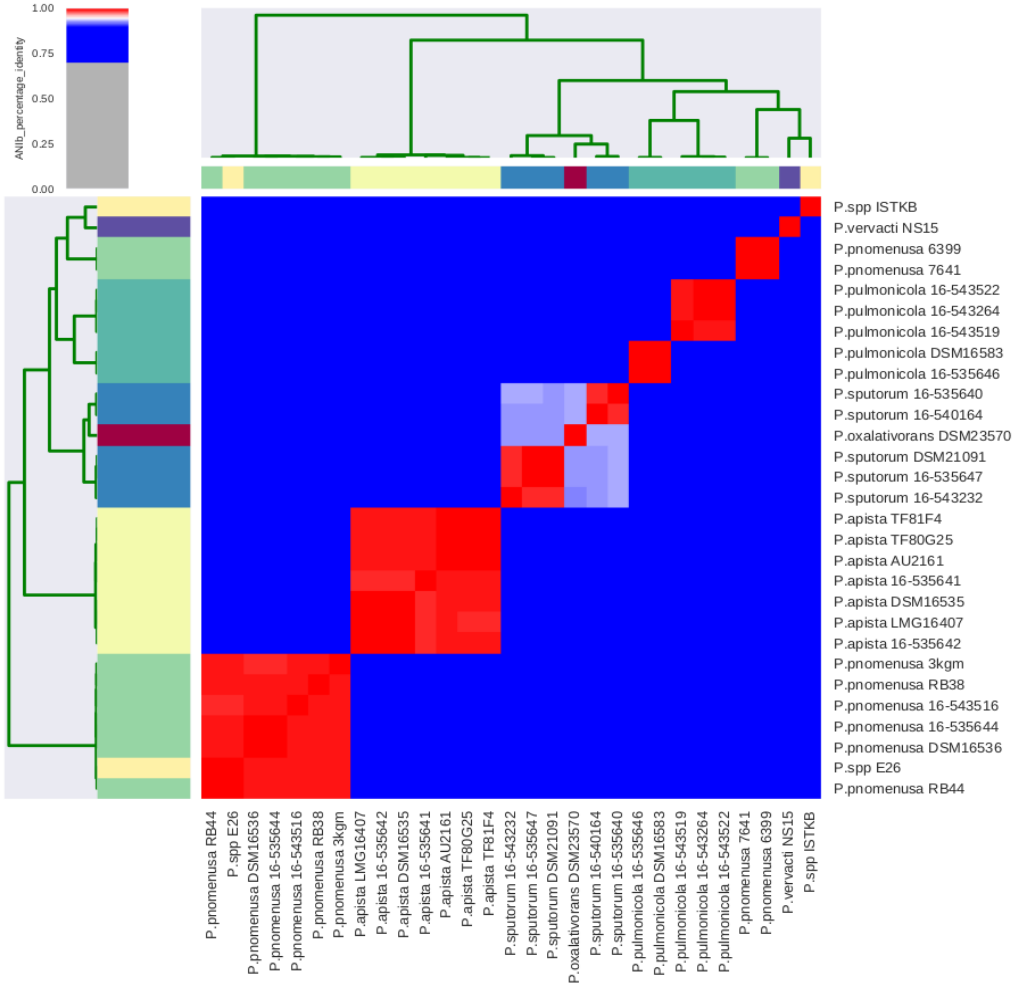
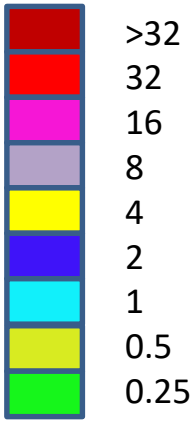
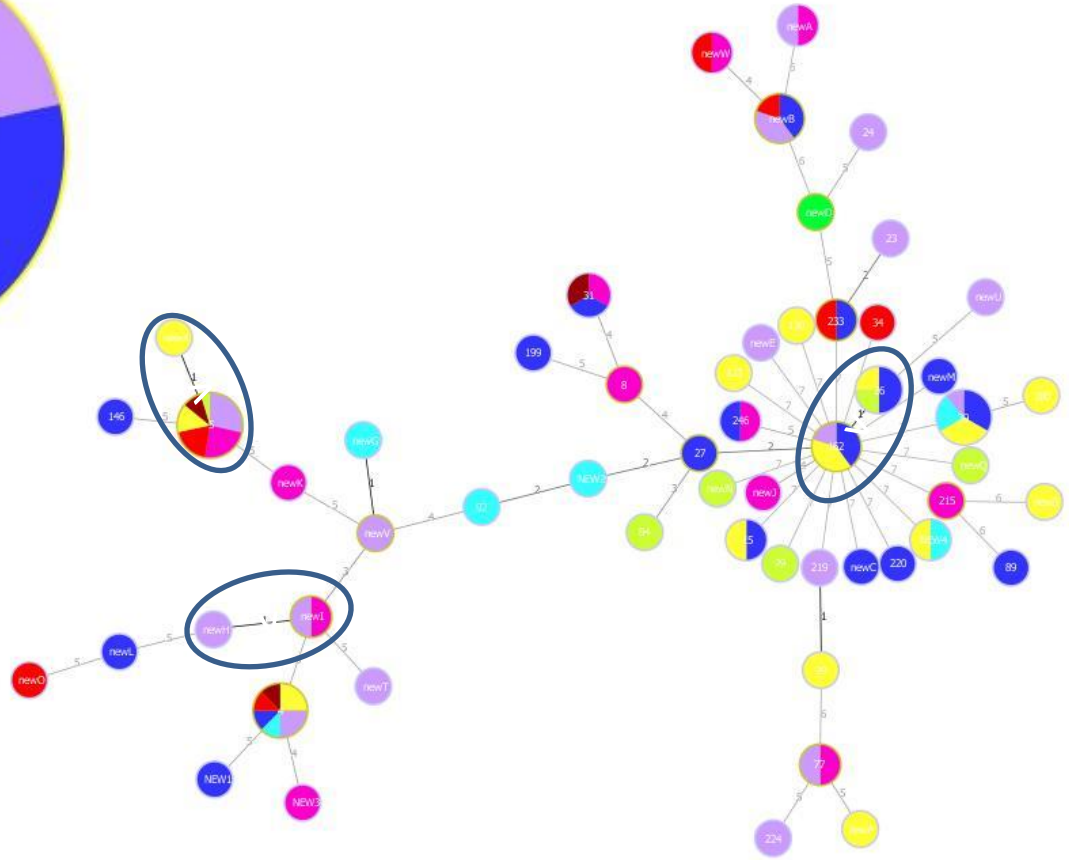


Biclustering based on percentage of ANI using ANIb method for all 29 *Pandoraea* isolates that were analyzed in this study.

Minimum Spanning Tree
Stenotrophomonas ST vs ciprofloxacin MIC





Minimum Spanning Tree
Pseudomonas ST vs murevapadin MIC_{50-90}

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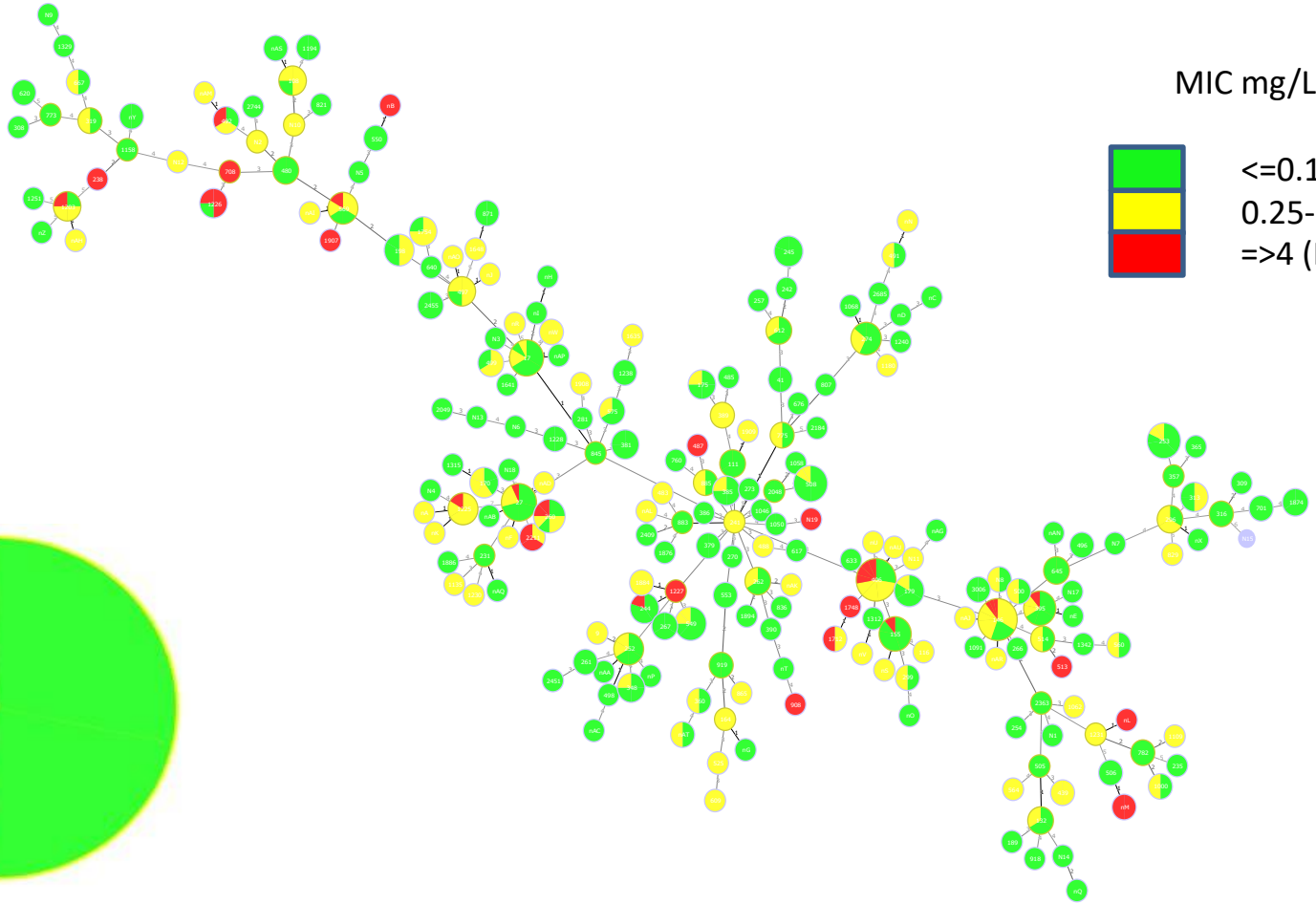
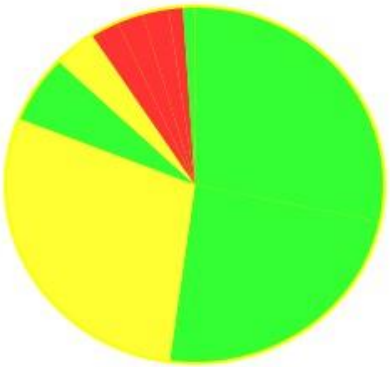


MIC mg/L

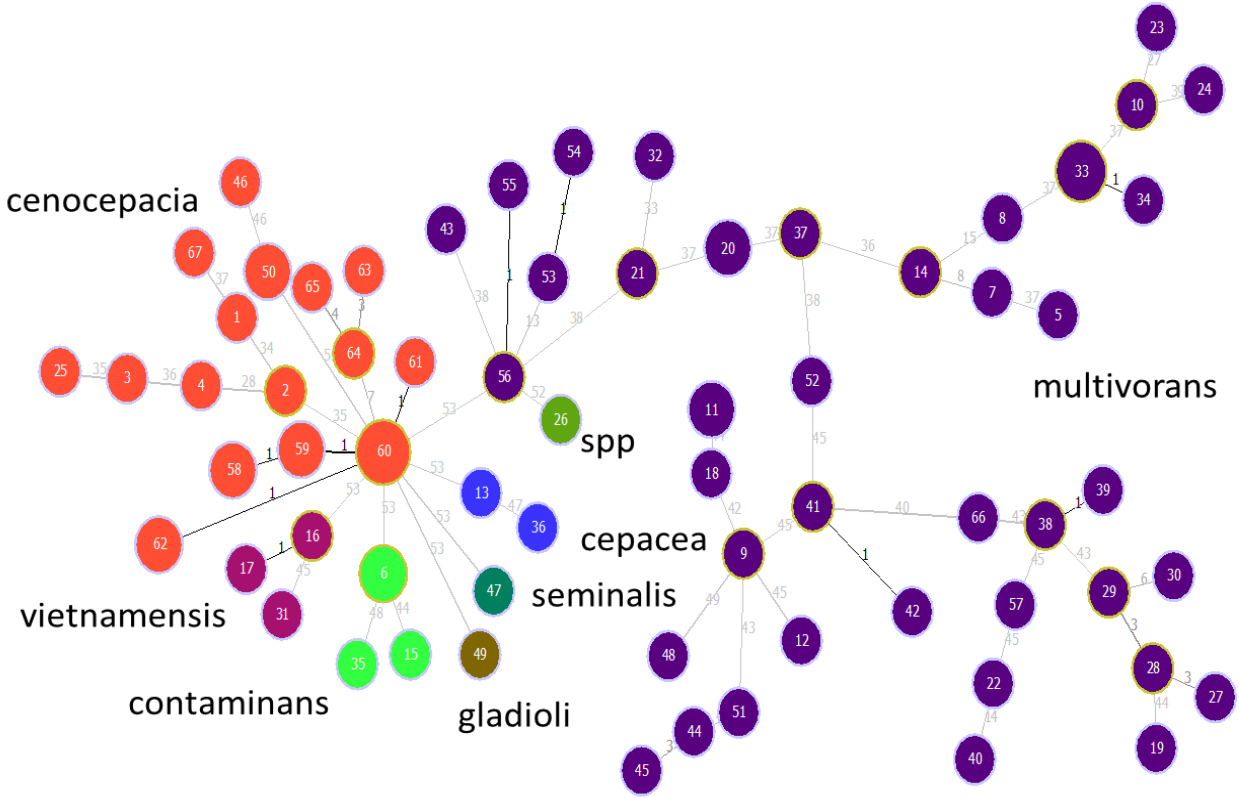
<=0.12 (MIC_{50})
0.25-2
=>4 (MIC_{90})



Minimum Spanning Tree

Burkholderia

Minimum spanning tree based on wgMLST analysis of 79 *Burkholeria* isolates from iABC project. Isolates are represented by circles proportional to the no. of sequences. Colors represent species and numbers of branches represent allelic differences between isolates



Conclusions WGS, thus far

- A lot of information can be obtained from the data, e.g.:
  - Current taxonomy of species within genus *Pandoraea* may need revision.
  - *Stenotroph., Achrom., Burkhold.:* diverse collection, many novel STs and alleles.
  - Murepavadin MIC distribution appears to be random.
- Manuscripts currently in preparation:
  - Genome submission *Haemophilus haemolyticus* strain
  - Analysis of *Pandoraea* genomes and proposal for new taxonomy
  - Draft Genome Sequence strain 16-537536 (BE) – relation to *P. koreensis* group
- Plans: Classic MLST available, core genome MLST, acquired resistance genes
  - Prepare manuscripts for:
    - *Haemophilus:* BLNAR genotype; ß-lactam susceptibility
    - *Achromobacter, Stenotrophomonas, Ralstonia, Burkholderia*
    - *Pseudomonas:* analysis with suceptibility; murepavadin MIC vs genes/SNPs
  - Use *Pseudomonas* collection to aid development phage therapy (outside iABC)

CF mouse models

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- Aims in iABC:
  - Development of chronic infection model in β-ENaC mice
    - Overexpress airway-specific epithelial Na-channels, mimicking CF lung
  - Compare acute with chronic model of infection, and, if possible, establish predictive value for inhaled antibiotic therapy
  - Determine effect of murepavadin in mouse models of infection
  - Produce 'white paper' outlining best practice guidelines for pre-clinical trials of novel nebulised antimicrobials.

Preclinical models for inhaled therapy

- Validated inhaled delivery of tobramycin using a nose-only aerosol system (inExpose; SciReq).
  - Exposure time
  - Exposure rate
  - Delivered dose
- Compared efficacy of inhaled and systemic delivery of tobramycin to treat *P. aeruginosa* infection
- Established dose and duration required for bacterial clearance
- Compared efficacy of model using inbred and outbred strains of mice
- Established new chronic infection model in β-ENaC mice

Nebulised antibiotics in acutely infected WT mice: comparable clearance to systemic delivery

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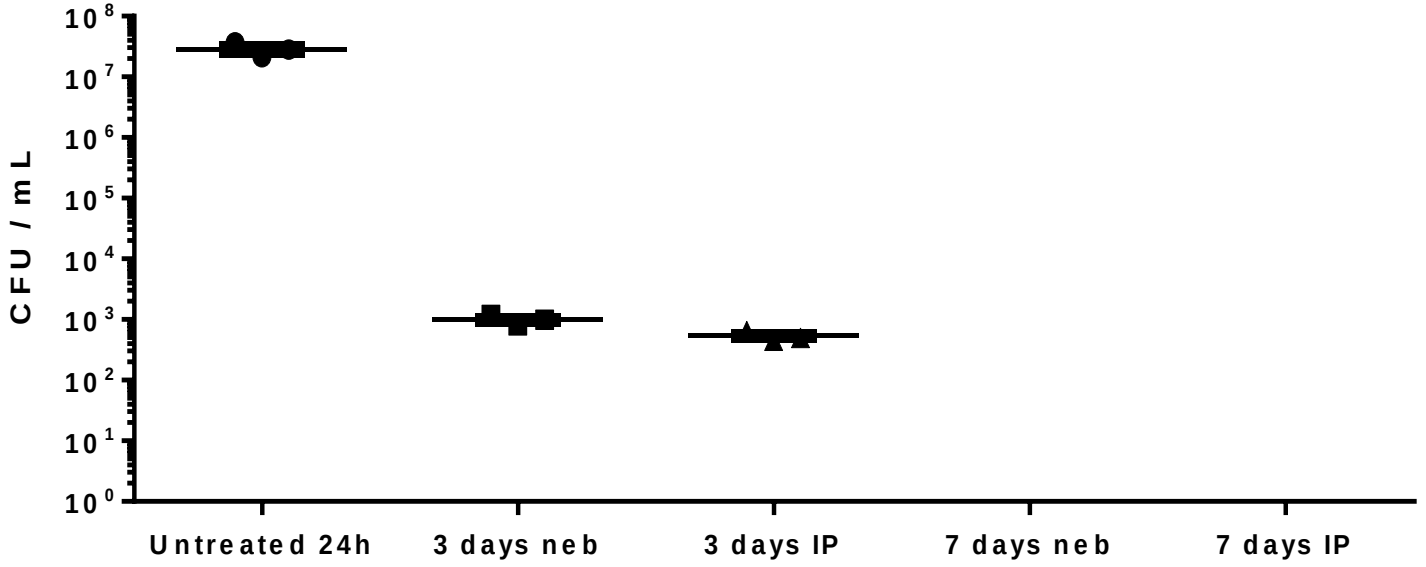
7 days of once daily 10mg/kg tob

Mice culled and CFU in lung and nalt quantified



Bacterial rebound after clearance: useful model to study bacterial reservoirs and resistance development?

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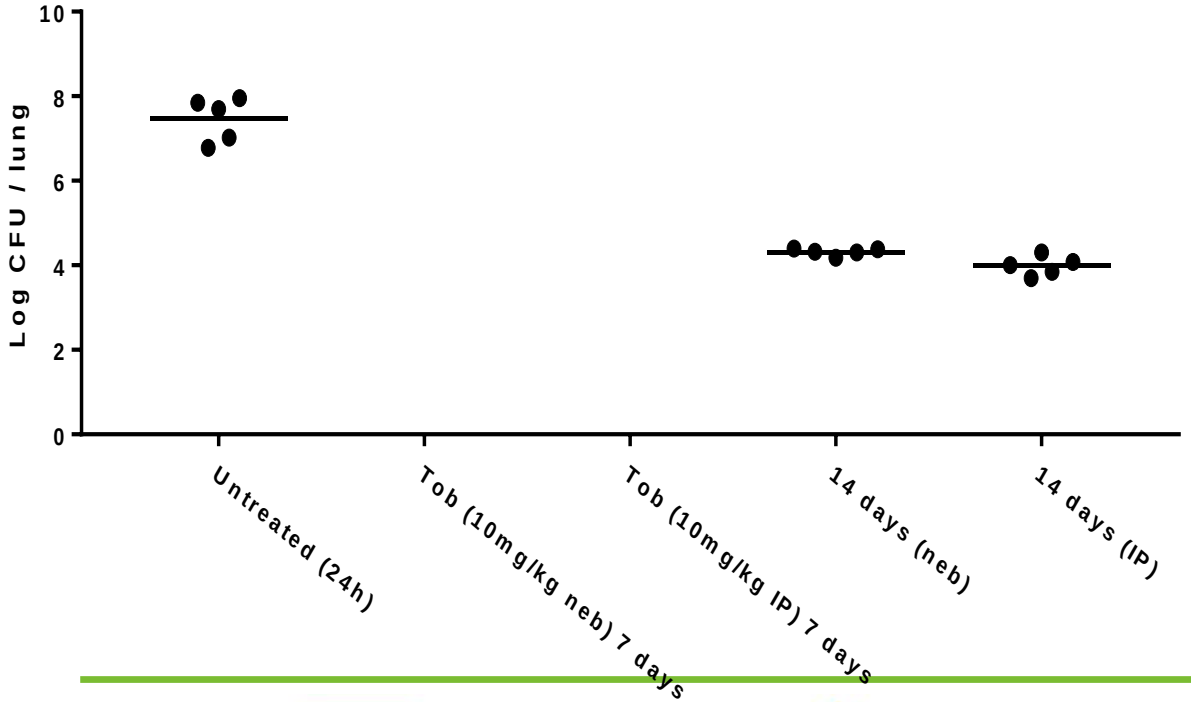
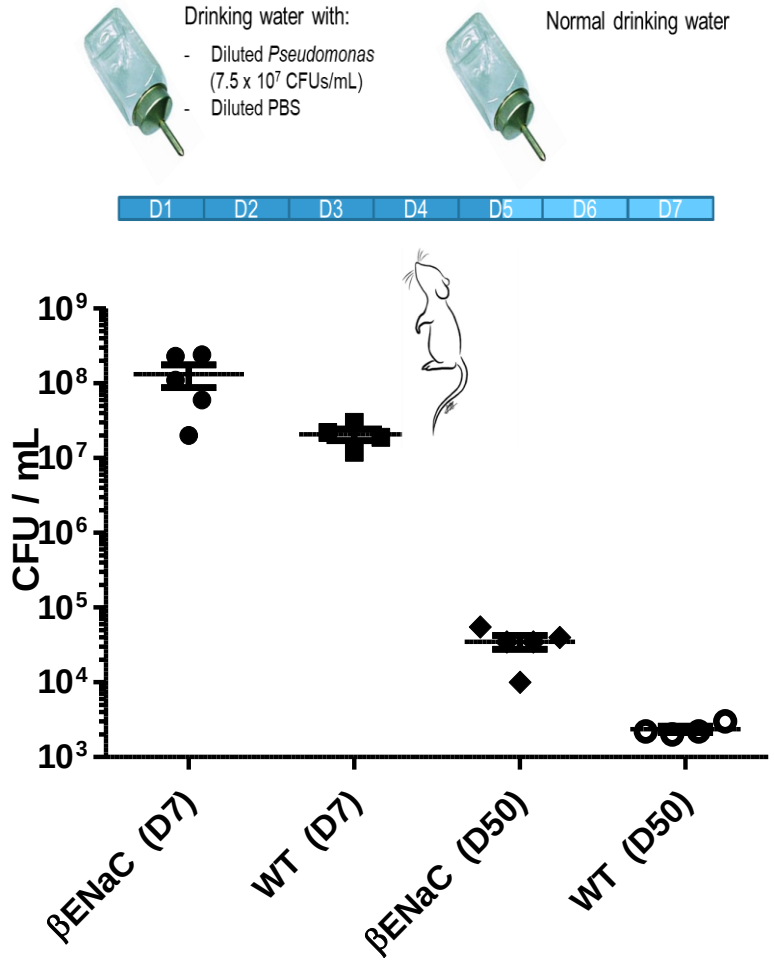
7 days of once daily 10mg/kg tob

7 days no treatment

Mice culled and CFU in lung and nalt quantified



New, biologically relevant, chronic infection model has been established



- This novel model allows establishment of longer term chronic infection in both wild type or and transgenic (BENaC - CF/Bronchiectasis phenotype) animals
- Chronic infection does not require artificial embedded material
- **Model now used to evaluate the efficacy of nebulised antibiotics in chronic infection.**

Upcoming work on animal models

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- Assess the ability of inhaled antibiotics to clear chronic infection using new β-ENaC model (PAO1)
  - Determine efficacy of clearance of clinical isolates of *P. aeruginosa*
  - Test POL7080 in chronic model
- Look at in vivo impact of POL7080 on host microbiome
- Adapt the chronic infection model to incorporate co-infection
  - Proposed to use *Staphylococcus aureus* as opposed to *Burkholderia*
- Produce “white paper” on pre-clinical trails w/ inhaled antibiotics

Biofilm models of the CF lung

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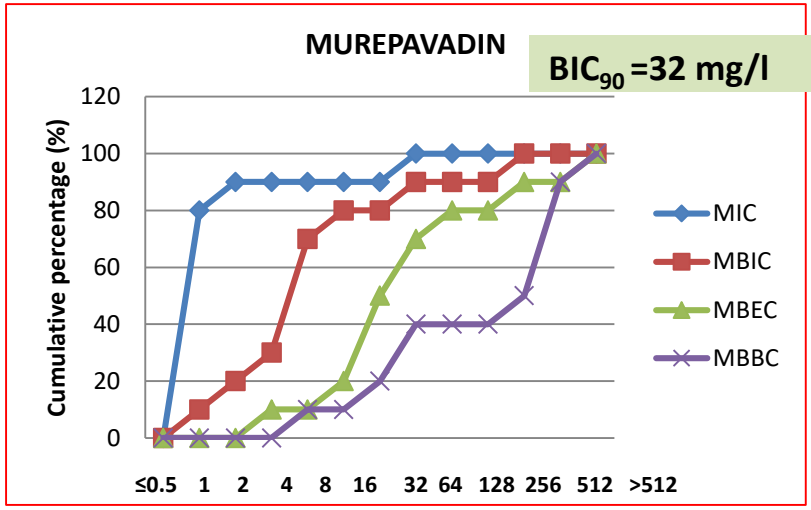
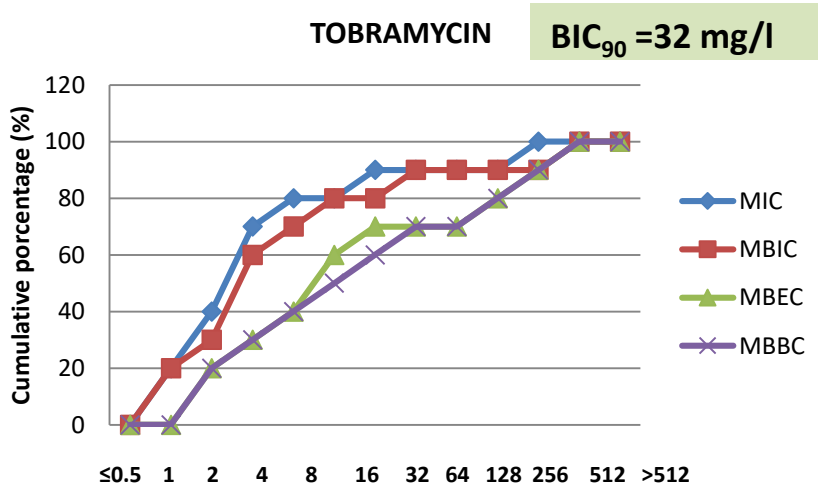
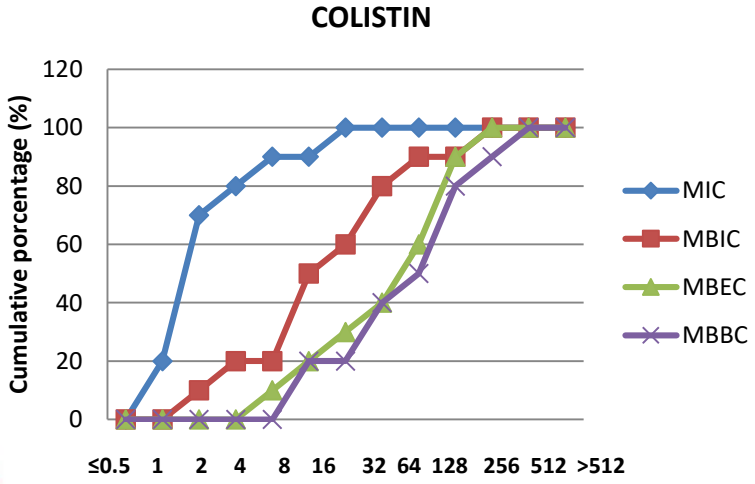
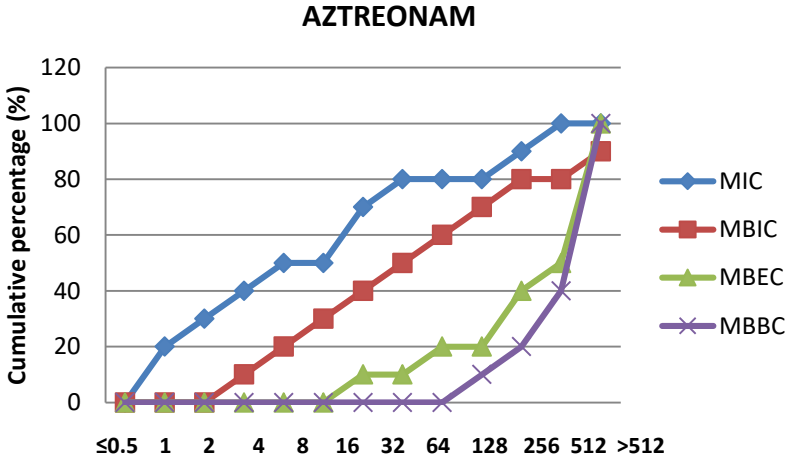
- Aims:
  - Develop an open biofilm model
  - Compare outcomes of open models with conventional testing, closed models, and – if possible – clinical outcomes
  - Provide input for rationale behind susceptibility testing and breakpoints for inhaled therapy
  - Test activity of murepavadin in biofilm

P. aeruginosa biofilm models: Closed model CALGARY









P. aeruginosa biofilm models: Open model BIOFLUX

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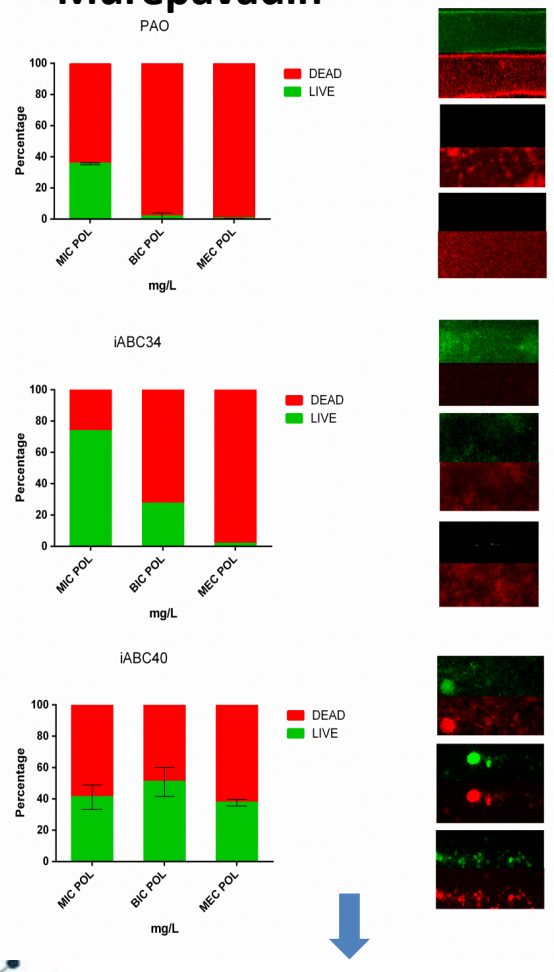
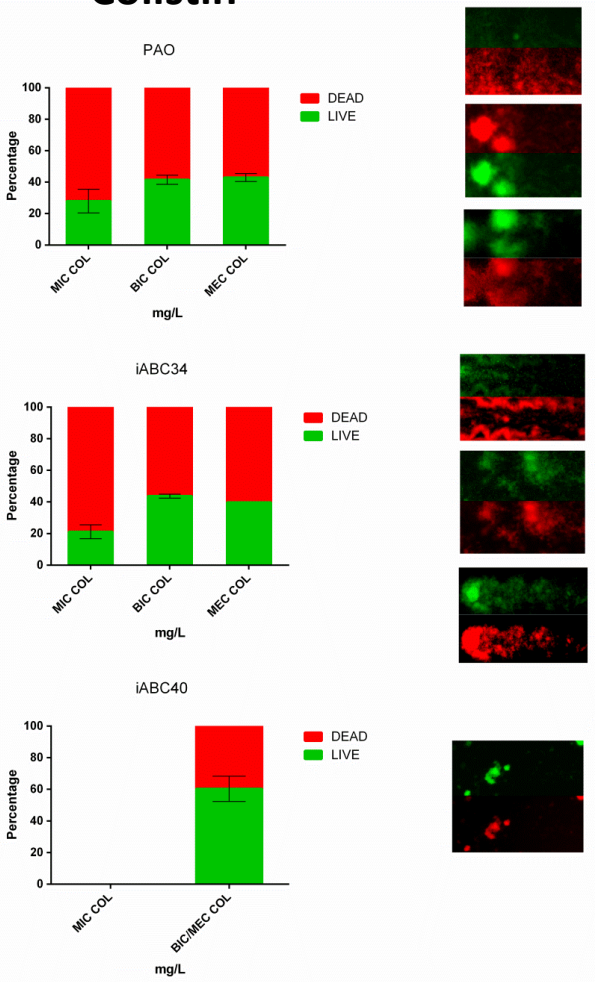
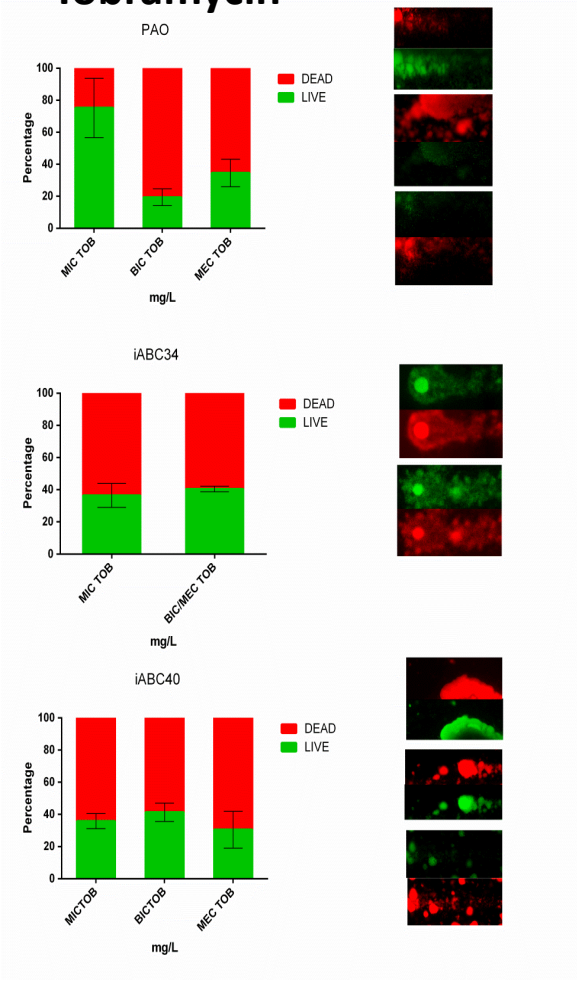
Murepavadin



Colistin



Tobramycin



Good activity on *in vitro* biofilms at the biofilm inhibitory and eradication concentrations

Work done...

- **Díez-Aguilar *et al.*** Antimicrobial susceptibility of non-fermenting Gram-negative pathogens isolated from cystic fibrosis patients. **Int J Antimicrob Agents 2018.**
- **Díez-Aguilar *et al*.** Use of Calgary and Microfluidic BioFlux Systems To Test the Activity of Fosfomycin and Tobramycin Alone and in Combination against Cystic Fibrosis *Pseudomonas aeruginosa* Biofilms. **Antimicrob Agents Chemother 2017.**
- **Díez Aguilar *et al***. In vitro antimicrobial activity of tobramycin, colistin, aztreonam and the new antibiotic murepavadin (POL7080) against cystic fibrosis *Pseudomonas aeruginosa* growing in biofilms. **IMI 10th Symposium 2018.**
- **Díez Aguilar *et al.*** Antimicrobial susceptibility against a collection of *Pseudomonas aeruginosa* recovered from cystic fibrosis and bronchiectasis patients. **ECCMID 2018.**

Working on...

- Sequentiation of *P. aeruginosa* murepavadin mutants
- Murepavadin susceptibility in artificial sputum
- Study of antibiotic combinations with murepavadin
- Murepavadin breakpoints for inhaled therapy

iABC WP2 (+ WP7) conclusions

- BAL30072 was a promising antibiotic for inhalation therapy
  - Good activity against CF pathogens, in particular *Burkholderia*
  - Suitable drug for both nebulization and DPI
  - Development halted due to toxicity in PhI and preclinical models
- Encouraging results in scientific objectives, continued in WP7:
  - Biofilm model (open)
  - Genomic analysis of CF pathogens (1000 strains sequenced)
  - Development of animal model of chronic CF lung infection
  - Analysis of feasibility separate breakpoints inhaled therapy (murepavadin)

WP7 Murepavadin: Introduction I

iABC
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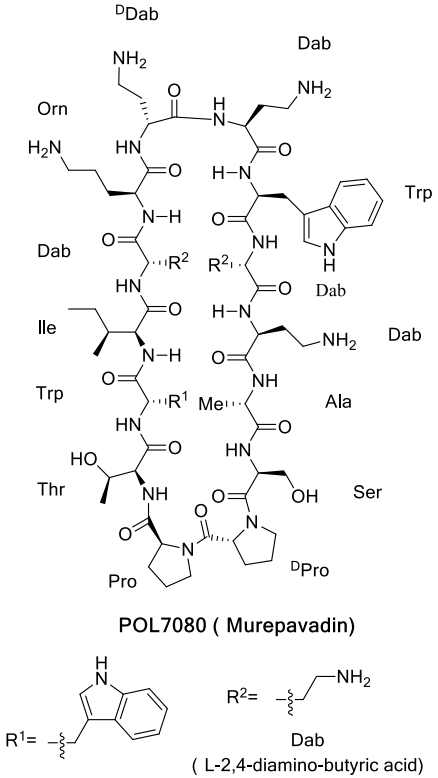
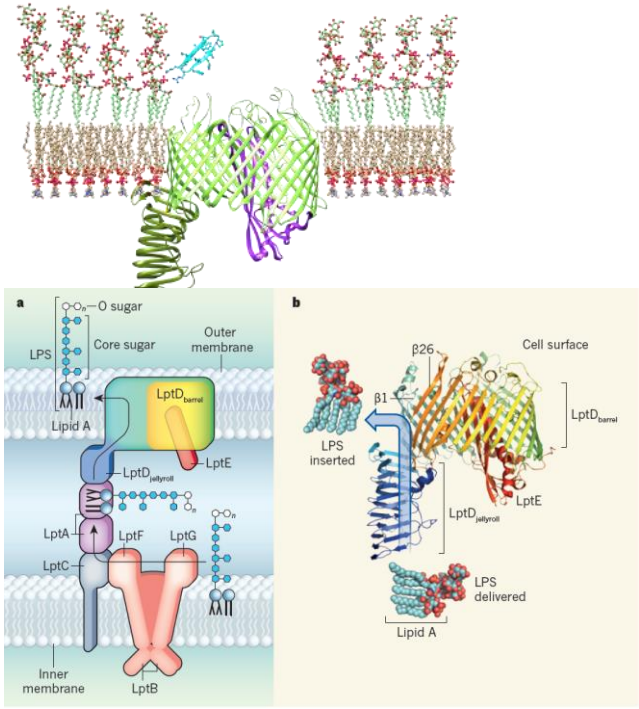
LptD identified as Outer Membrane protein target for Murepavadin



Target LPS and LptD

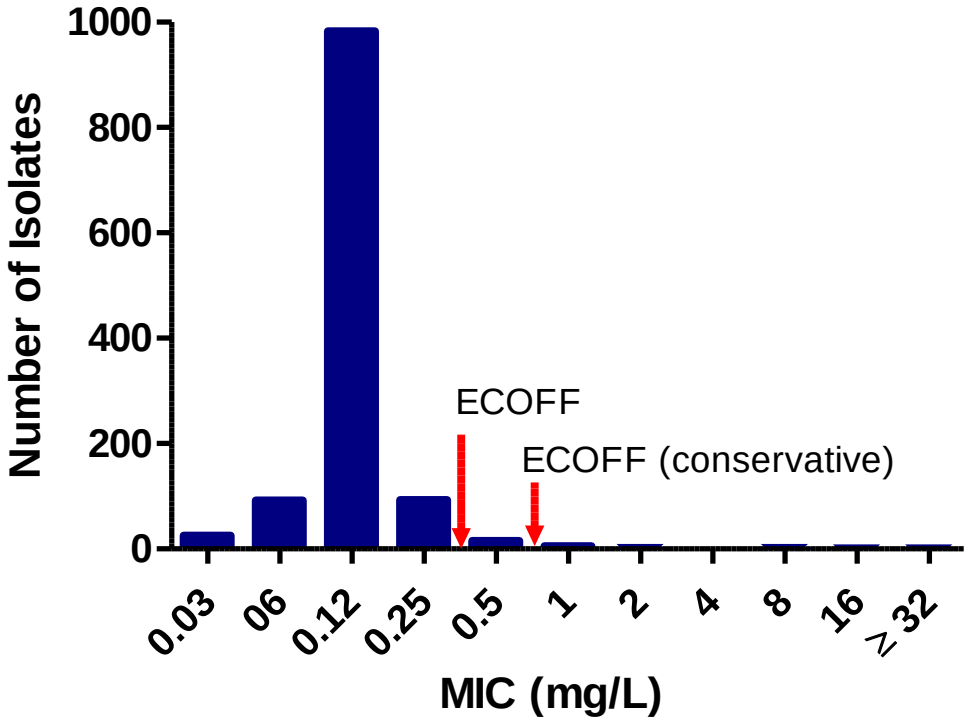


N. Srinivas et al. *Science* **2010**, *327*, 1010-1013; R. E. Bishop, *Nature* **2014**, *511*, 37-38; S. Qiao et al. *Nature* **2014**, *511*, 108-111; Dong et al. *Nature* **2014**, *511*, 52-56

WP7 Murepavadin: Introduction II

iABC
inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis

There is little difference between geographies or MDR and non-MDR MIC distributions



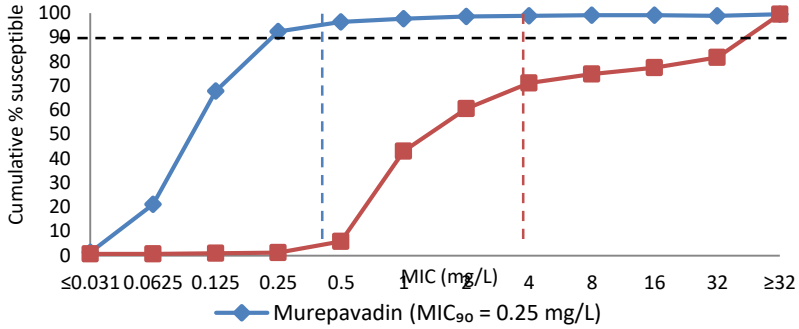
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32
n=1219	25	92	983	93	15	5	2	0	2	1	1
Cum %	2.1	9.6	90.2	97.9	99.1	99.5	99.7	99.7	99.8	99.9	100.0

Surveillance data (n=1219) from Europe and USA (2014) and China (2012-2013) including 28% MDR pathogens

WP7 Murepavadin: Introduction III

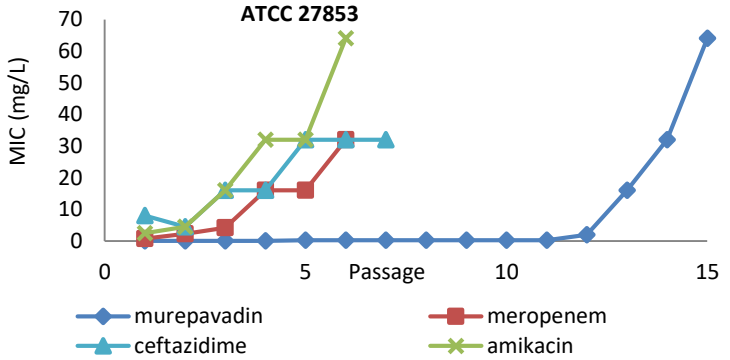
- New MoA / New class (OMPTA)[1]
- Pathogen specific: antibiotic stewardship
- Bactericidal
- Highly potent including MDR[2] / XDR[3]
- High lung penetration
- Low resistance potential
- QIDP[4] (add. 5 year exclusivity) and fast track status
- Targeted at nosocomial pneumonia

Highly potent and superior coverage
Cumulative susceptibility on 785 XDR isolates



EUCAST breakpoints	▪ Murepavadin target MIC = 0.5mg / L ▪ Ceftolozane / tazobactam > 4mg / L

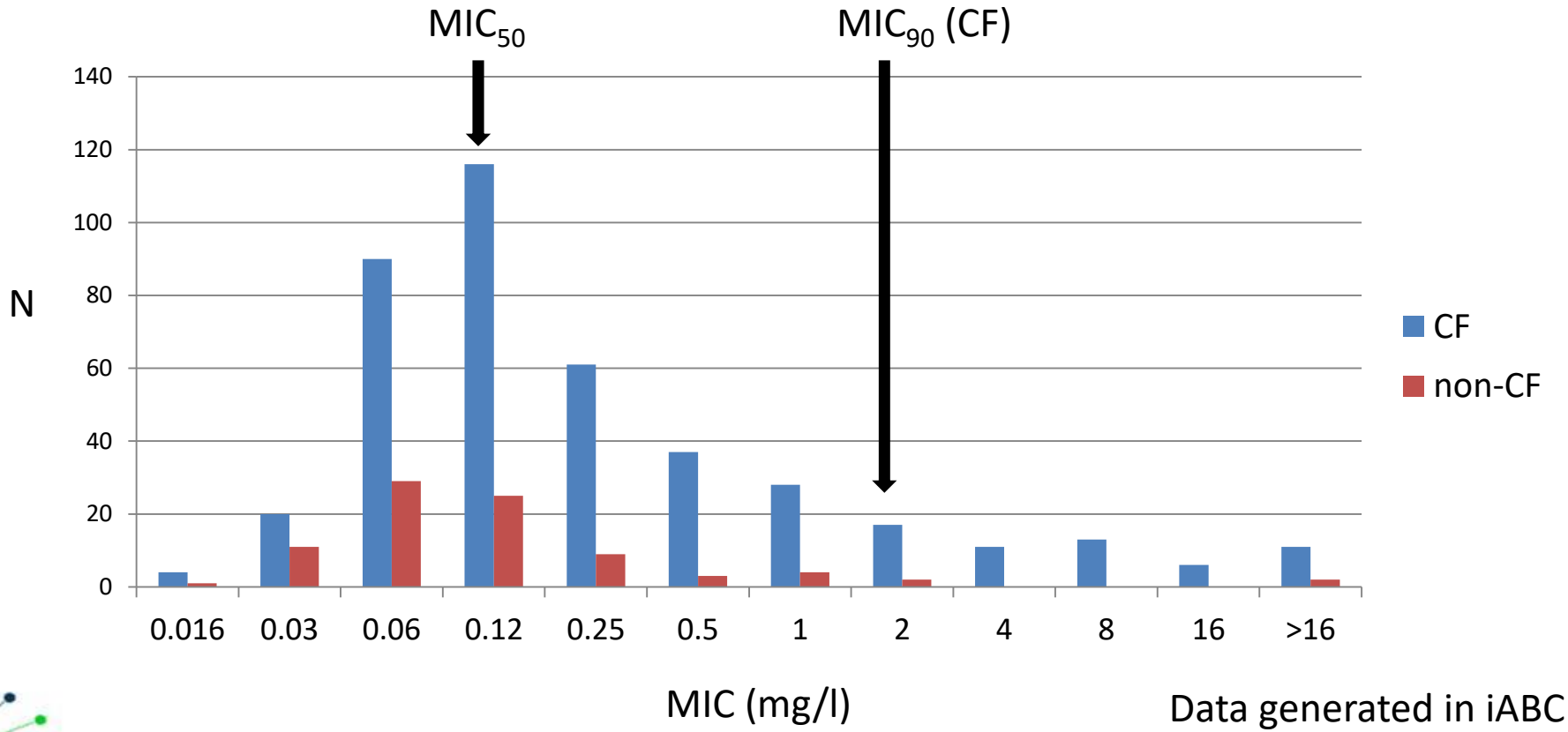
2-3x slower development of resistance Resistance development: serial passage



EUCAST breakpoints	▪ meropenem >8 mg/L ▪ ceftazidime >8 mg/L ▪ amikacin > 16 mg/L

Notes:
1 Outer Membrane Protein Targeting Antibiotic
2 Multidrug-Resistant
3 Extensively Drug-Resistant
4 Qualified Infectious Disease Product and fast track designation granted for treatment of VABP due to Pseudomonas aeruginosa; 5 years of additional exclusivity

MICs murepavadin vs *P. aeruginosa* in CF



Data generated in iABC

CF-strains: MIC_{50} and MIC_{90} vs literature data

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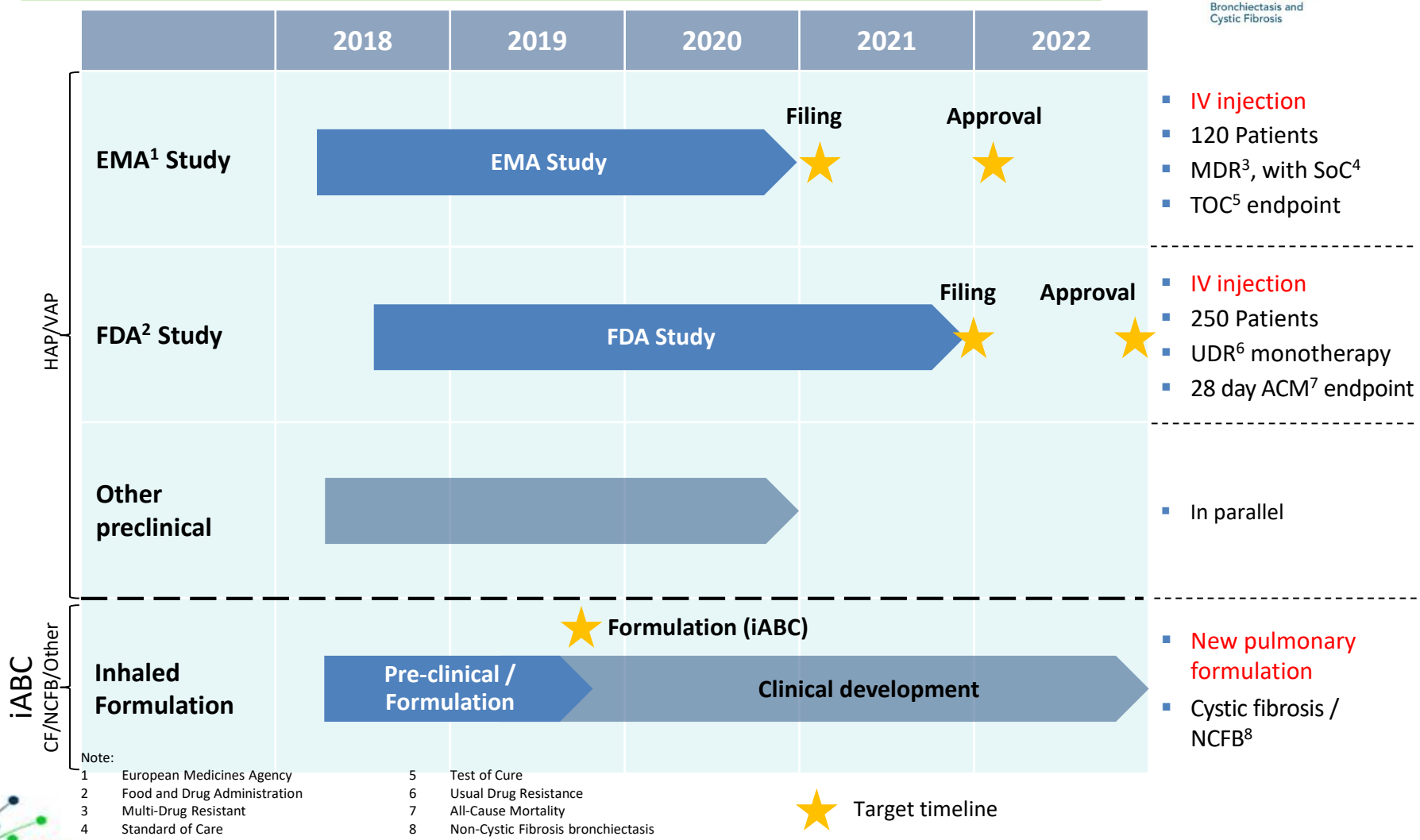
iABC data compared to Sader e.a. AAC 2018 and Sader e.a. JAC 2018

	Murepavadin		Ceftazidime		Ceftolozane-TZB		Piperacillin-TZB		Meropenem	
	MIC50	MIC90	MIC50	MIC90	MIC50	MIC90	MIC50	MIC90	MIC50	MIC90
iABC, 522 isolates	**0.12**	**2**	2	64	1	2	4	128	0.25	16
iABC, 417 CF isolates	**0.12**	**2**	2	64	1	2	4	128	0.25	16
SENTRY: 1219 isolates, AAC	**0.12**	**0.12**	2	>32	.	.	4	128	0.5	16
SENTRY: 167 XDR, AAC	**0.12**	**0.25**	>32	>32	.	.	128	>128	16	>16
SENTRY: 785 XDR, JAC	**0.12**	**0.25**	32	>32	2	>32	>64	>64	16	>32

Non-CF isolates in iABC, MIC_{90} 0.5 mg/l

Murepavadin most active antibiotic on a per weight basis

Murepavadin Development



Note:

1 European Medicines Agency
2 Food and Drug Administration
3 Multi-Drug Resistant
4 Standard of Care
5 Test of Cure
6 Usual Drug Resistance
7 All-Cause Mortality
8 Non-Cystic Fibrosis bronchiectasis

★ Target timeline

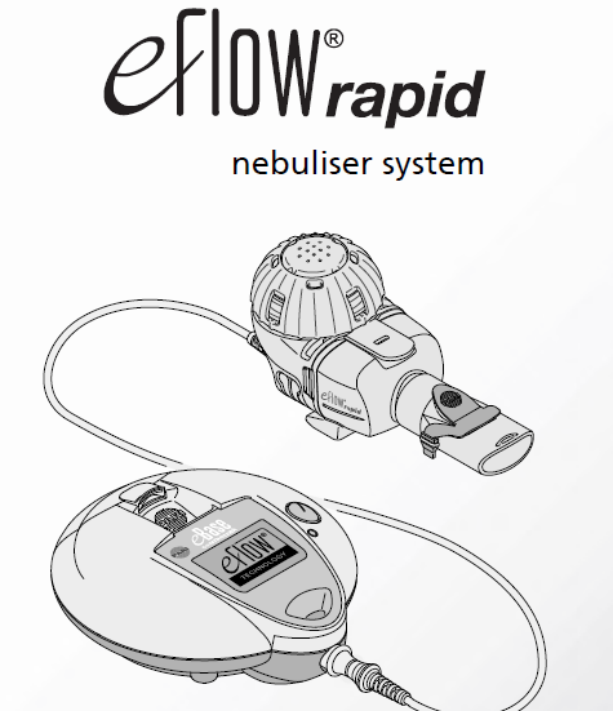
WP7 Inhaled murepavadin: CMC I

- Uni Groningen: Development of POL7080 powder for reconstitution to obtain solution for aerosol nebulization with eFlow nebuliser
- 4 salts tested (acetate, hydrochloride, L-tartrate, D-tartrate)
- TPP was fulfilled using acetate salt and PARI 30mesh head
- Drug Product deemed suitable for Ph1 (Taste to be assessed)

Parameter	Results
Drug form	POL7080 as acetate salt
Drug concentration after rec. with WFI	100 mg/mL
Reconstitution in WFI	60 sec manual shaking
pH	5
Osmolality	353 mOsm/kg
TOR (Total Output Rate)	250 mg/min, resulting in 500mg emitted dose in 20 minutes
FPF (Fine Particle Fraction) <5 µm	>90%
Fraction 1.1 to 3.1 µm	> 50%
Solution Stability	Stable at RT for 6 hours

WP7 Inhaled murepavadin: CMC II

- PARI GmbH:
  - confirm results of UniGroningen (powder for reconstitution)
  - verify feasibility of a ready-to-use liquid aerosol system with eFlow nebuliser
- Activities started in Nov 2018
- Goals:
  - Confirm results of UniGroningen (powder for reconsti
  - Develop liquid system for nebulization with eFlow
  - Optimise dosing head (30 mesh and 40HO mesh)
  - Verify Aerodynamic Particle Size Distribution (APSD) with NGI tester and Breath Simulator
  - Verify drug solution stability at 2-8°C and RT



WP7 Inhaled murepavadin: CMC III

- Uni Groningen: development of Dry Powder Inhaler (DPI) in parallel
- Activities started in Nov 2018
- Particle size reduction of POL7080 powder <5 µm by different methods:
  - Top-down by Micronisation (air-jet milling or ball-milling)
  - Bottom-up by Spray-Drying
- Powder dispersion by high dose inhalers (target 50mg dose):
  - Twincer
  - Cyclops

E: Twincer®

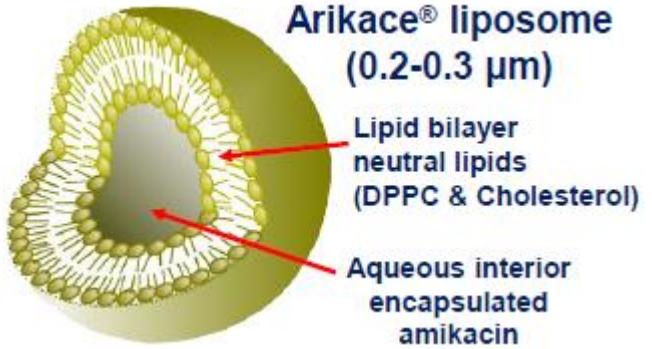
F: Cyclops®

WP7 Inhaled murepavadin: CMC option

POL7080 Liposomes for pulmonary administration

- To be developed as option
- Advantages for CF and Bronchiectasis:
  - Further reduce systemic distribution
  - Avoid local irritation in airways
  - Improve lung targeting and retention
  - Improve biofilm penetration
  - Reduce vascular degradation
  - Mask bad taste

- Potential Partners:
  - MicroSphere
  - Evonik



Example Arikace® (Amikacin Liposomes)

Inhaled MUREPAVADIN preclinical

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- Multiple dose PK study with Pari eFlow nebulizer
  - In life phase ends Dec 12
  - Suitability of formulation
  - Dose optimisation and PK profile
  - Initial tolerability assessment in lung
- Efficacy study
  - Nebulized Murepadavin will be tested at 3 doses in murine lung infection models with *P. aeruginosa*
  - Efficacy will be measured as reduction of bacterial colonies counts
  - A control strain and 2-3 clinical isolates will be tested

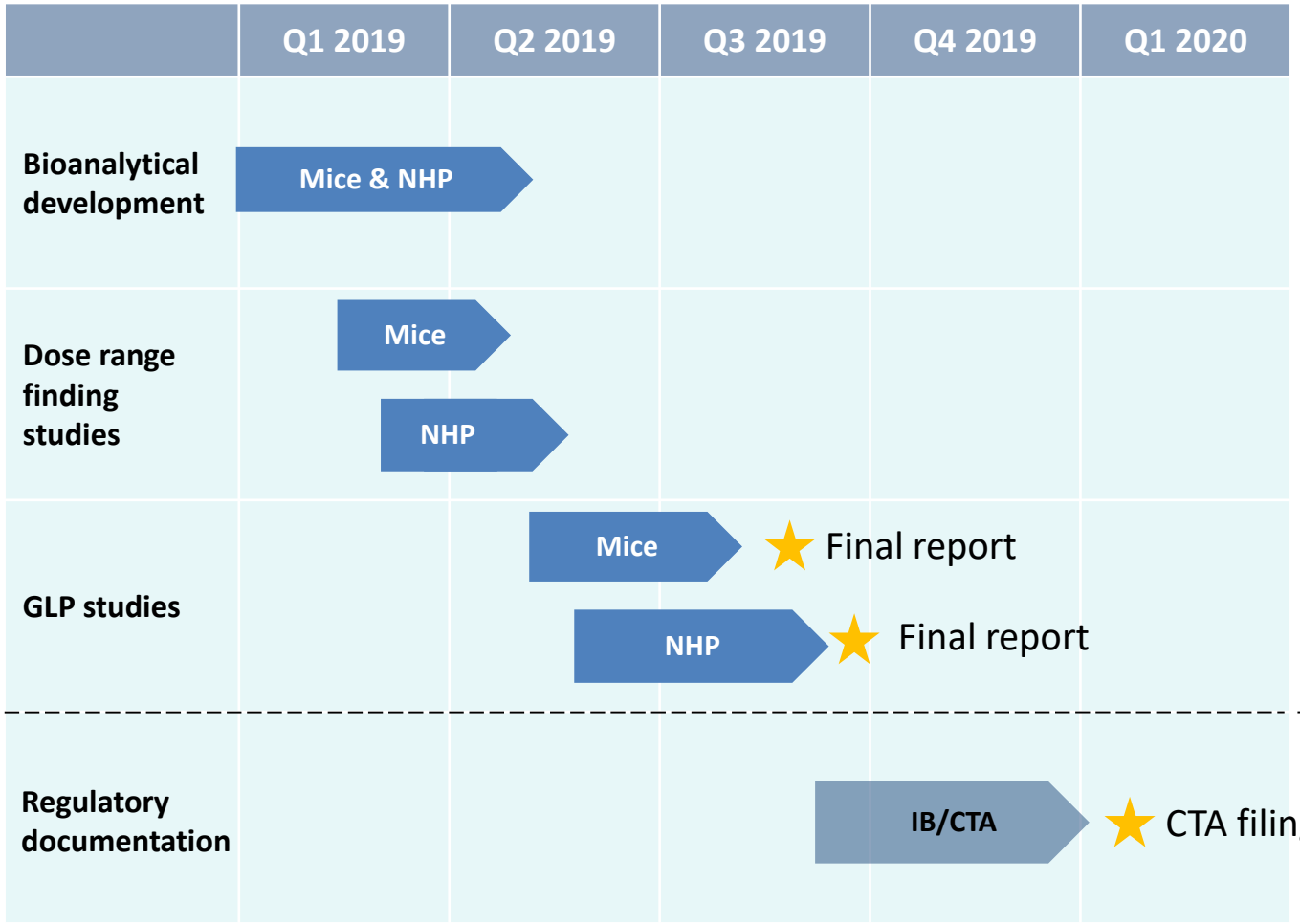
Inhaled MUREPAVADIN preclinical

iABC
inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis

- IND/CTA enabling preclinical package scheduled
  - Tender process completed and CRO selected
  - Dose range findings studies in mice and NHP start April 2019
  - 4-week GLP studies in mice and NHP start July 2019
  - Safety pharmacology starts July 2019
  - Reporting complete October 2019

- Clinical Trial Application on time

WP7 Inhaled Murepavadin: Preclinical Gantt



WP8 – Polyphor Clinical Programme (1)

iABC
inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis

Work Package 8 (led by Damian Downey, QUB)

- Details of study will be refined based on preclinical results and following advice from regulatory authorities (CHMP and FDA)
- task will begin as soon as POL7080 is formulated for inhaled delivery with eFlow and pharmacology and pre-clinical safety has been assessed

Goal: **deliver POC**

Consider small SADs and roll over into MAD/CF pts

- Phase 1a: **SAD / HV**
- Phase 1b: **SAD run in CF followed by MAD / POC**

WP8 – Polyphor Clinical Programme (2)

Phase Ia: PK and safety study in healthy subjects (PI: Stuart Elborn), as per current DOW

- single-centre, double-blind, randomised controlled single ascending dose (SAD) study in healthy subjects (n=24)
- determination of the maximum tolerated dose (MTD) and assessment of safety/tolerability and plasma PK of inhaled POL7080
- 3 dose levels administered over 3 days with 6 subjects on POL7080 and 2 subjects on placebo in each of the 3 cohorts
- inhaled POL7080 will be administered at a daily low, medium (=predicted) or high dose based on PK/PD estimations
- the maximal tolerated dose will be determined based on adverse events and respiratory function tolerance

WP8 – Polyphor Clinical Programme (3)

iABC
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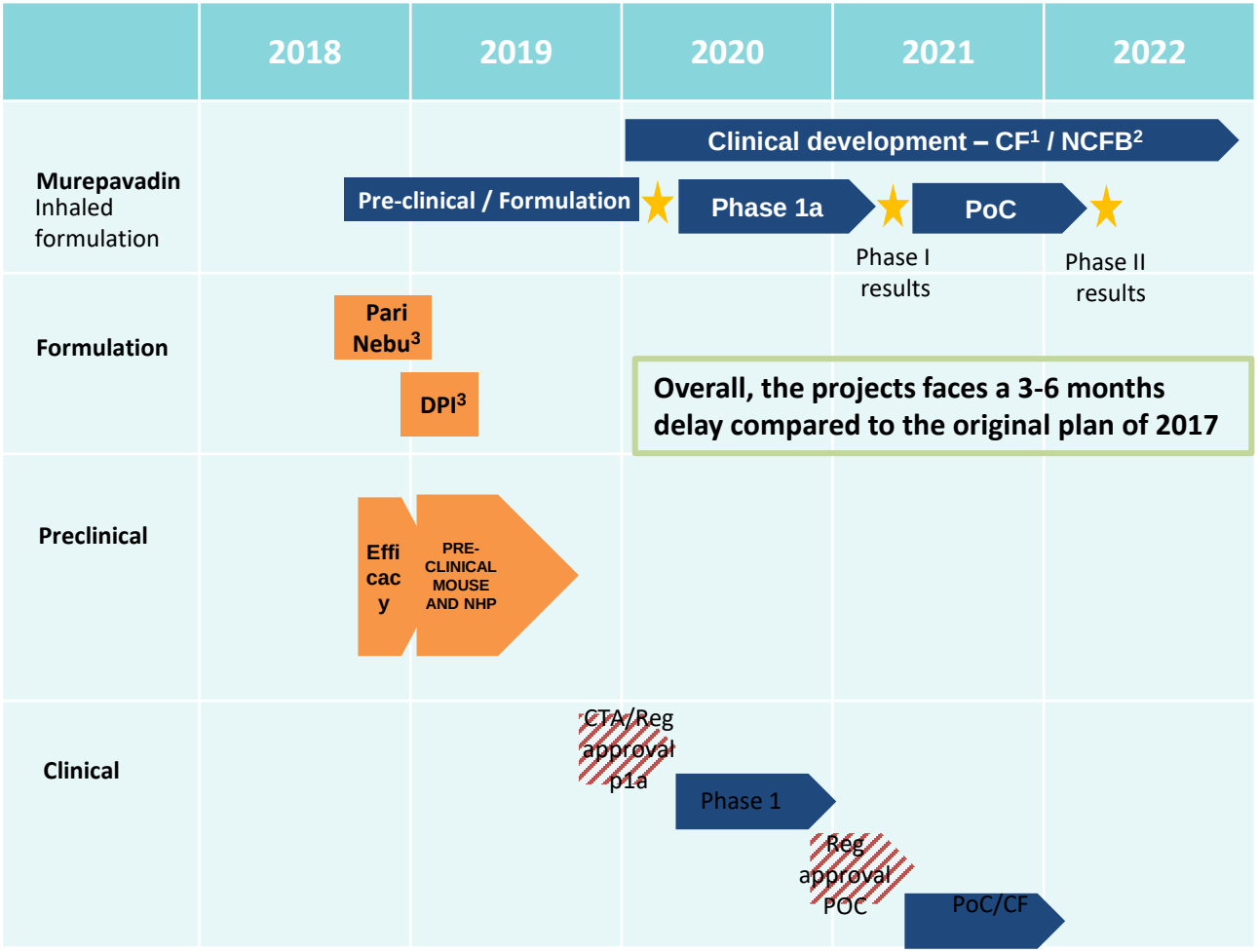
Phase Ib: PK, safety & Proof of Concept (POC) study in CF patients, as per current DOW

- SAD/MAD/POC study in 48 CF adults (≥18 years) colonised with Pa
- 3 subsequent dose cohorts with 12 subjects on POL7080 administered for 28 days based on PK/PD estimations from the previous SAD study in healthy volunteers
- primary end-points: safety/tolerability with plasma and sputum PK including PK/PD modelling of inhaled POL7080
- secondary endpoints: (to assess efficacy) change in sputum CFU at 2 weeks, lung function and QOL. MIC will be determined at baseline, day 28 and day 56.
- novel endpoints will include lung function assessed by LCI, sputum microbiome and inflammatory biomarker analyses
- Proposed study design: POL7080 is introduced to the current recommended 28 days on/off cycle of TIP alternate month.

iABC- Murepavadin inhaled - Timelines



Summary: Progress within IMI project

iABC
inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis

- Development of inhaled murepavadin
  - In vitro susceptibility (MIC and biofilm) determined
  - In vivo efficacy and inhalation dosages established (intra-tracheal application)
  - Nebulized formulation selected
  - Nebulizer selected
  - Preclinical toxicology package determined and vendor selected

Results thus far support further development of inhaled murepavadin

- Scientific
  - Open biofilm model operational
  - In vivo β-ENaC mouse model operational
  - WGS finished, analysis of data started

Summary: Next steps within IMI

iABC
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- Development of inhaled murepavadin
  - Pre-clinical toxicology
  - Regulatory approval
  - Phase I
  - Phase II
- Scientific
  - (Further) analysis of WGS data
  - Further development and analysis of open biofilm model
  - Further development β-ENaC mouse model (and testing murepavadin)
  - Report on breakpoint development for inhaled therapy

Summary: Risks of WP7 and WP8

- Timelines very ambitious from the start. Currently: delay of 3-6 months from original timelines. Intention is to make time up in preclinical toxicology and submissions.
- However, further delay in following stages clinical development can never be excluded.
- Results from other clinical studies with murepavadin may impact on development of inhaled therapy.

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inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis

Work Package 5

James Chalmers

University of Dundee

WP5 objectives: EU wide registry for bronchiectasis

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Original Scope

- To develop an EU-wide registry for BE, aligning existing and nascent national networks and providing the framework for joint working, data sharing and collaboration
- To provide comprehensive data on the epidemiology, natural history and treatment of BE in Europe, including the exploitation of existing BE datasets
- To achieve synergies with non-EU registry initiatives for BE, including the US BE research registry of the COPD foundation
- To contribute to the generation of evidence-based recommendations on the management of patients with BE
- To make data from the EU BE registry accessible to the scientific community at large
- To disseminate knowledge and communicate results at international conferences and in peer reviewed publications
- To ensure that the EU BE registry is sustainable beyond the life of this project

Challenges in forming a European registry

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ecfs

Variable definitions

Inclusion/exclusion criteria

Variable quality control

Huge cost of administering registries in every country

Solution:
Alignment of data fields and definitions at set-up

Single data collection platform

Shared administrative set-up= sustainability

Partners in the Registry

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BRONCHIECTASIS RESEARCH REGISTRY
A COPD FOUNDATION INITIATIVE

IRIDE
ITALIAN REGISTRY OF ADULT BRONCHIECTASIS

ERS EUROPEAN RESPIRATORY SOCIETY

RRNI
RESPIRATORY RESEARCH NETWORK INDIA

PROGNOSIS

iABC
inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis

ELF EUROPEAN LUNG FOUNDATION

imi
Innovative Medicines Initiative

BRONCH-UK

LUNG FOUNDATION AUSTRALIA
"When you can't breathe... nothing else matters"™

International Bronchiectasis Registry Network

Europe
United States
India
Australia

Bronchiectasis biobank and translational research "hub"

Clinical Trials Network

Registry study design

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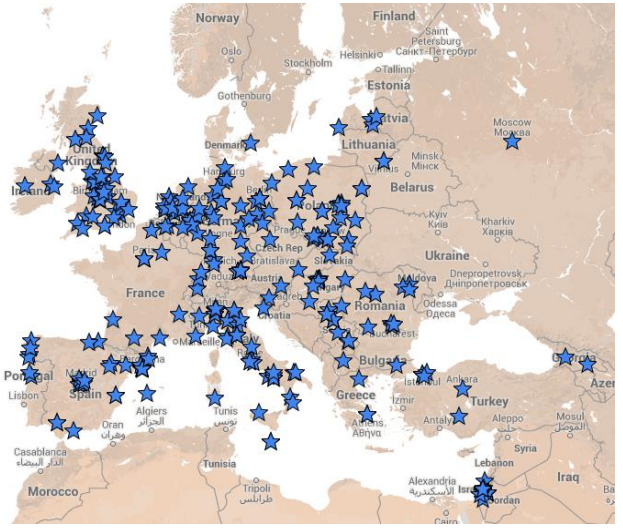
Screening
A clinical history consistent with bronchiectasis (cough, chronic sputum production and/or recurrent respiratory infections)
AND
CT scan of chest demonstrating bronchiectasis (bronchial dilation) affecting ≥1 lobes

Exclusion criteria
Bronchiectasis due to unknown cystic fibrosis
Age <18 years
Patients who are unable or unwilling to provide informed consent
Traction bronchiectasis due to interstitial lung disease without clinical bronchiectasis
Previous lung or heart-lung transplantation

Recruitment

Demographics	Aetiology testing
Comorbidities	Microbiology
Lung function and morbidity	Radiology
Quality of life	Treatments

Annual follow-up
Mortality, cause of death
Repeat data for all fields above



5 years- annual follow-up

Open

High level of data quality control

EMBARC executive group








EMBARC steering committee

Scientific committee

Topic working groups










International advisory board

Patient advisory group

EMBARC

The European Bronchiectasis Registry

Welcome, editor.

Home | About EMBARC | NEWS | RESEARCH | EDUCATION | Registry Documents | EMBARC Registry

Innovative Medicines Initiative

The European Bronchiectasis Registry is supported by the European Union Innovative Medicines Initiative under the "New Drugs for Bad Bugs" programme, to help facilitate the development of new antibiotics against Gram-negative infections

EMBARC is a pan-European network committed to promoting clinical research and education in bronchiectasis, through sharing of protocols, research idea and expertise. Central to this project is the creation of the European Bronchiectasis Registry, a collaboration open to all investigators around Europe caring for patients with bronchiectasis.

Latest News

EMBARC passes 2000 patients enrolled! February Newsletter is online

Feb 26 2016 9:00 AM

Congratulations to EMBARC investigators and members from 23 countries who have contributed to achieving the 2000th patient enrolled. This greatly exceeds our targets for the first year of recruitment. ...

Read More

January EMBARC newsletter is online

Jan 28 2016 10:04 AM

Latest Research

Quality standards for the management of bronchiectasis in Italy: a national audit

Aliberti S, Hill AT, Mantero M, Battaglia S, Centanni S, Cicero SL, Lacedonia D, Saetta M, Chalmers JD, Blasi F; SIP Bronchiectasis Audit Working Group. / Eur Respir J. 2016 Apr 13. pii: ERJ-00232-2016. doi: 10.1183/13993003.00232-2016.

Telomere Dysfunction and Senescence-associated Pathways in Bronchiectasis

Birch J, Victorelli S, Rahmatika D, Anderson RK, Jiwa K, Moisey E, Ward C, Fisher AJ, Soyza AD, Passos JF / Am J Respir Crit Care Med. 2016 Apr

Join EMBARC

EMBARC is an open group and free to join.

For more information contact info@bronchiectasis.eu

Sign up at the registration page

Talk to us on Twitter!

Milestones and deliverables

Milestone No.	Milestone Description	Expected delivery date	Means of verification
M5.1	Regulatory and ethical approvals and registry start. Completion of eCRF.	M7	Approval and D5.2
M5.2	Publication of research Roadmap.	M13	D5.6
M5.3	Enrolment of first 1000 patients.	M14	Registry data reports
M5.4	Active participation of 20 European countries.	M14	Registry data reports
M5.5	Enrolment of 4000 patients from at least 20 EU Countries.	M26	Registry data reports
M5.6	Enrolment of 6000 patients.	M38	Registry data reports
M5.7	Secured external funding for sustainability of the registry over the long term.	M60	Funding letters received

Deliverable No.	Deliverable description	Nature (R, P or O)	Expected delivery date
D5.1	Alignment of proposed registry fields with international registries.	R	M6
D5.2	Completion of electronic CRF.	R	M6
D5.3	First patient enrolled into the registry.	R	M7
D5.4	Annual data reports.	R	M13, M25, M37, M49, M60
D5.5	Peer reviewed publications and abstracts.	R	M13, M25, M37, M49, M60
D5.6	Publication of research roadmap	R	M13

EMBARC

The European Bronchiectasis Registry

Welcome, editor.

Summary:

Completed Sections: 2
Incomplete Sections: 5

Not all sections are completed: you cannot submit the case

Demographic information updated succesfully.

Embarc Database CRF Case J2071

Back to list

Basic case information	Complete
Co-morbidities - Demographics and Background	Complete
Bronchiectasis background information	Draft
Aetiology and laboratory testing	Draft
Microbiology	Draft
Radiology	Draft
Respiratory Treatments	Draft
Additional information	

ERS EUROPEAN RESPIRATORY SOCIETY

Milestones and deliverables

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M5.5	Enrolment of 4000 patients from at least 20 EU Countries.	M26	Registry data reports
M5.6	Enrolment of 6000 patients.	M38	Registry data reports
M5.7	Secured external funding for sustainability of the registry over the long term.	M60	Funding letters received

Deliverable No.	Deliverable description	Nature (R, P or O)	Expected delivery date
D5.1	Alignment of proposed registry fields with international registries.	R	M6
D5.2	Completion of electronic CRF.	R	M6
D5.3	First patient enrolled into the registry.	R	M7
D5.4	Annual data reports.	R	M13, M25, M37, M49, M60
D5.5	Peer reviewed publications and abstracts.	R	M13, M25, M37, M49, M60
D5.6	Publication of research roadmap	R	M13

“The Roadmap”

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TASK FORCE REPORT
RESEARCH STATEMENT

CrossMark

Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration

Stefano Aliberti[1], Sarah Masefield[2], Eva Polverino[3], Anthony De Soyza[4,5], Michael R. Loebinger[6], Rosario Menendez[7], Felix C. Ringshausen[8], Montserrat Vendrell[9], Pippa Powell[2] and James D. Chalmers[10] on behalf of the EMBARC Study Group[11]

Affiliations: [1]School of Medicine and Surgery, University of Milan Bicocca, Clinica Pneumologica, AO San Gerardo, Monza, Italy. [2]European Lung Foundation, Sheffield, UK. [3]Fundaciò Clìnic, IDIBAPS, CIBERES, Hospital Clinic de Barcelona, Barcelona, Spain. [4]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK. [5]Bronchiectasis Service, Freeman Hospital, Newcastle upon Tyne, UK. [6]Host Defence Unit, Royal Brompton Hospital, London, UK. [7]Pneumology Service, Universitary and Polytechnic Hospital La Fe, Valencia, Spain. [8]Dept of Respiratory Medicine, Hannover Medical School, Member of the German Center for Lung Research (DZL), Hannover, Germany. [9]Bronchiectasis Group, Girona Biomedical Research Institute (IDIBGI), Dr. Trueta University Hospital, Girona, Spain. [10]College of Medicine, University of Dundee, Dundee, UK. [11]For a list of the EMBARC Study Group investigators see the Acknowledgments section.

Milestones and deliverables

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Milestone No.	Milestone Description	Expected delivery date	Means of verification
M5.1	Regulatory and ethical approvals and registry start. Completion of eCRF.	M7	Approval and D5.2
M5.2	Publication of research Roadmap.	M13	D5.6
M5.3	Enrolment of first 1000 patients.	M14	Registry data reports
M5.4	Active participation of 20 European countries.	M14	Registry data reports
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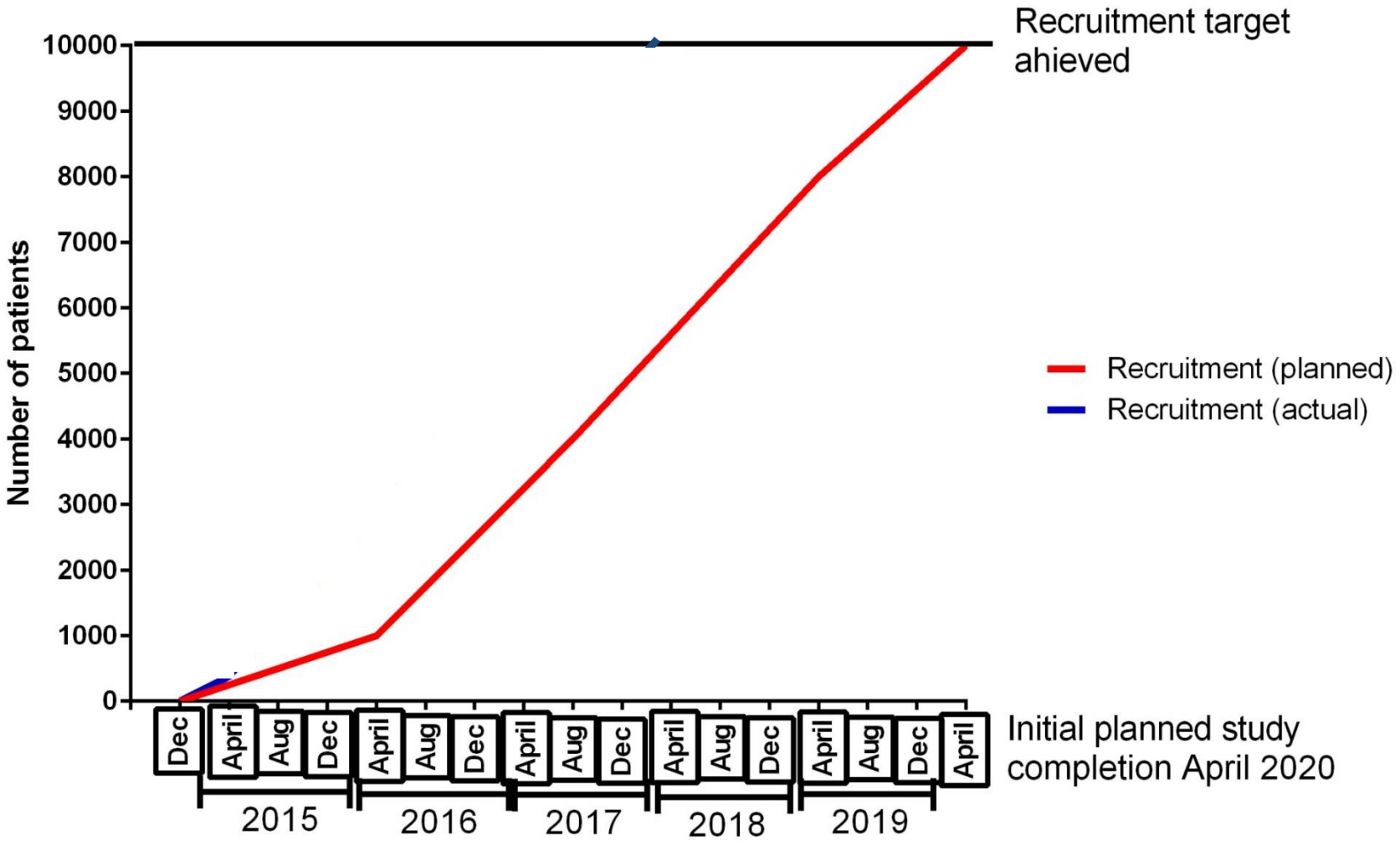
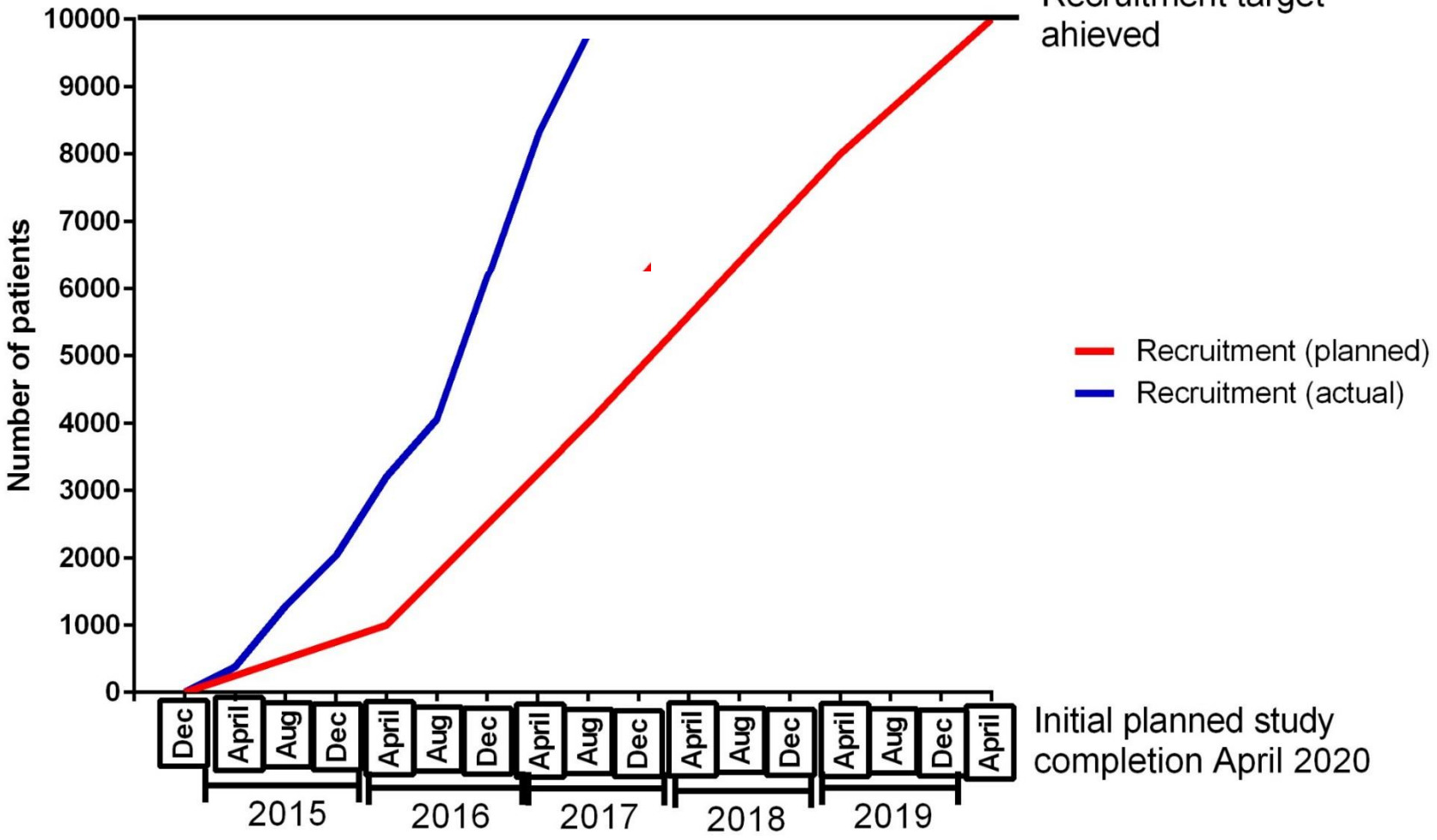
Recruitment



Recruitment



Most recent registry data

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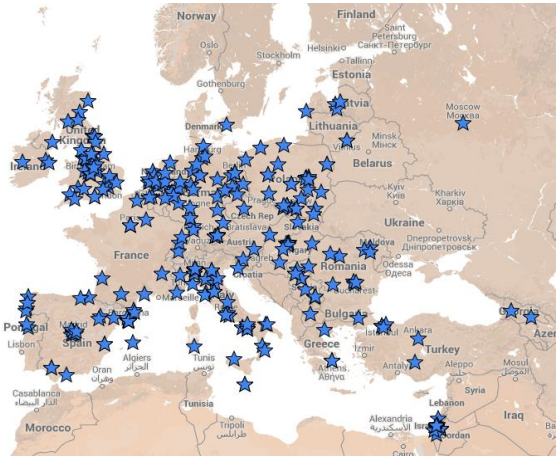
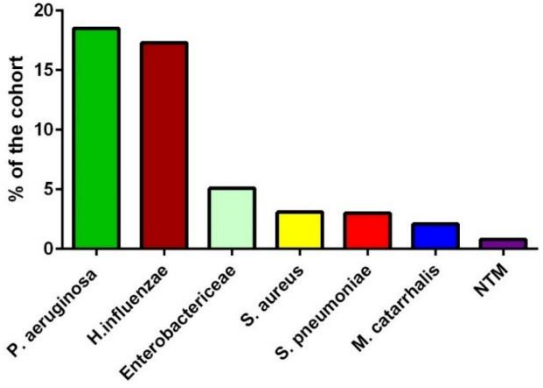
- 14,265 patients registered
- 27,502 unique records
- Nearly 80% eligible 1 year follow-up recording
- >60% eligible 2 year follow-up recording

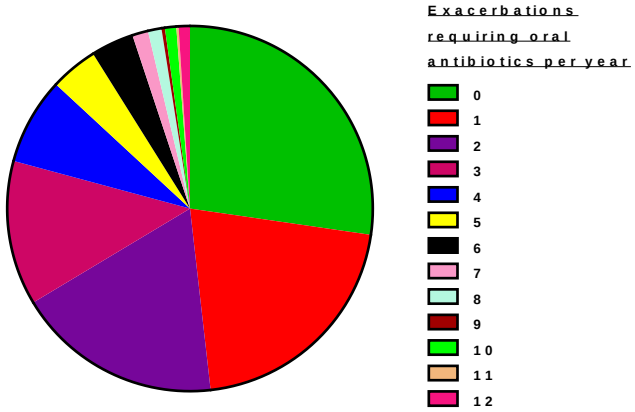


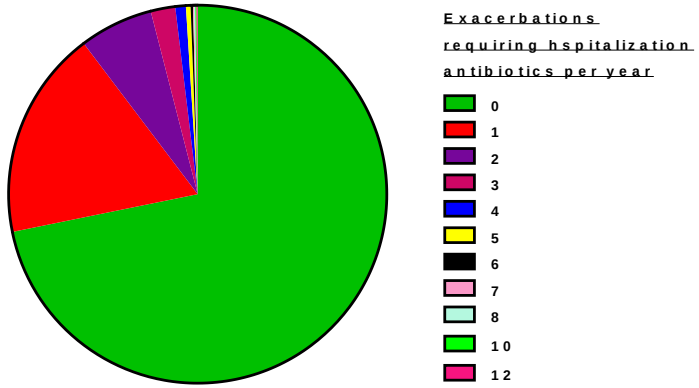
Patients enrolled: 11204
from **27 countries**

Demographics
58% female
Median age= 68 years
(IQR 58-75)

Never smoked =55.9%
Ex smoker= 38.3%

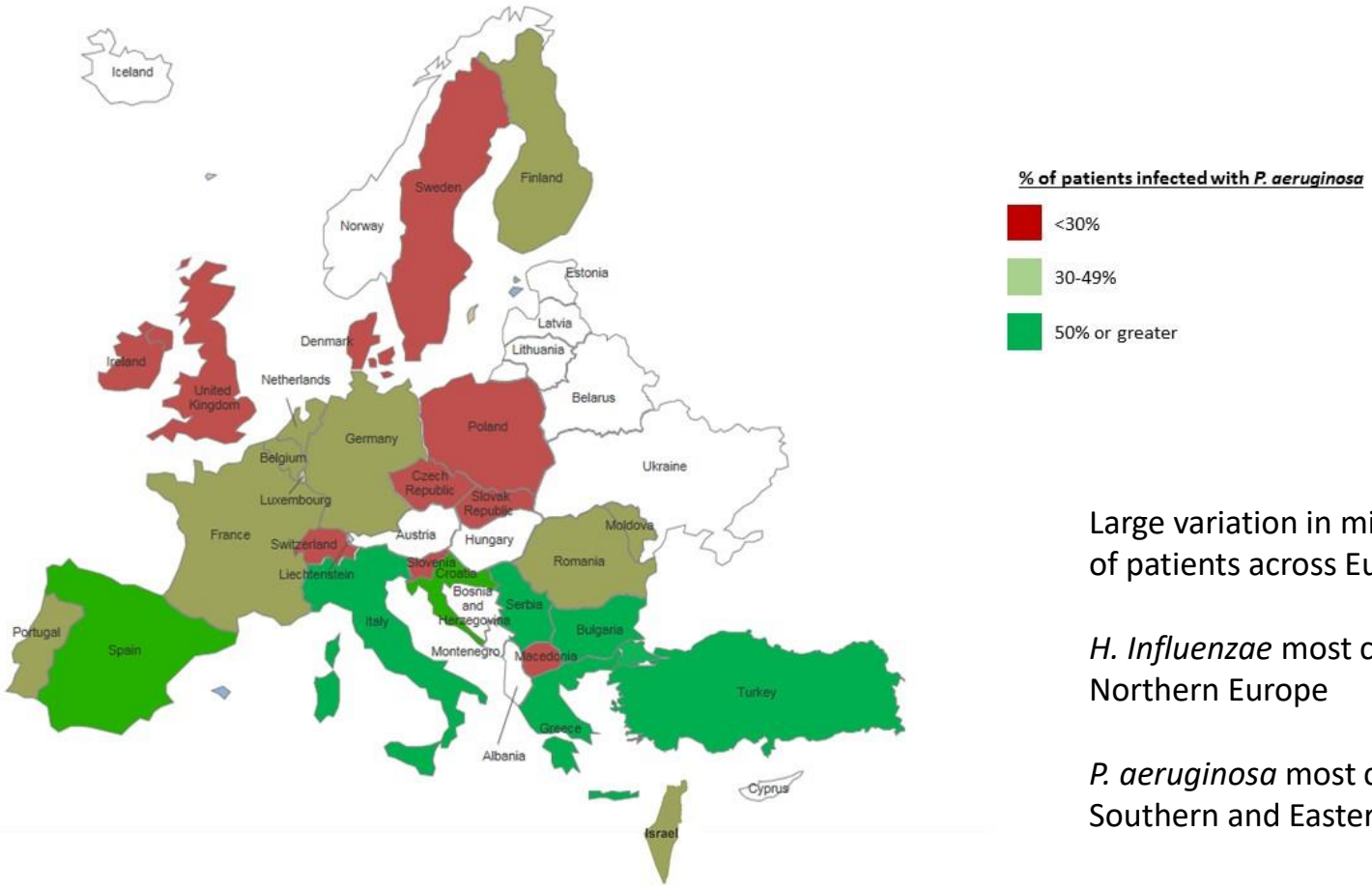






Chalmers et al. *ERJ Open Res.* 2016; 2: 81

P. Aeruginosa across Europe



Large variation in microbiology of patients across Europe

H. Influenzae most common in Northern Europe

P. aeruginosa most common in Southern and Eastern Europe

WP5 objectives: EU wide registry for bronchiectasis

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Original Scope

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Initial Data

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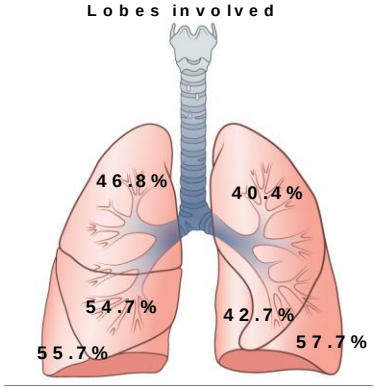

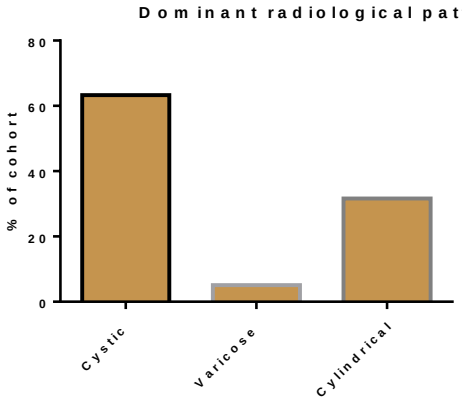

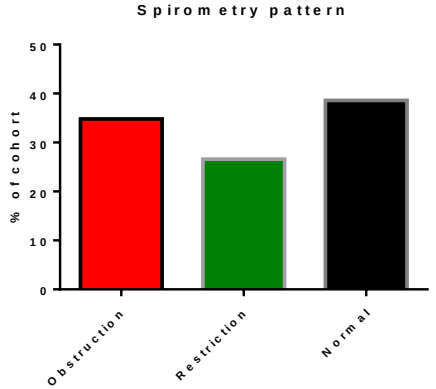

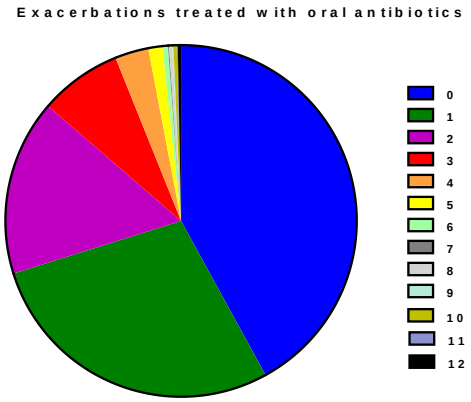

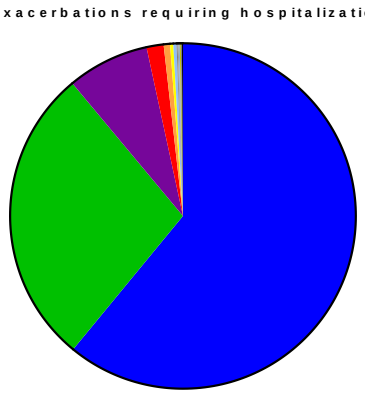

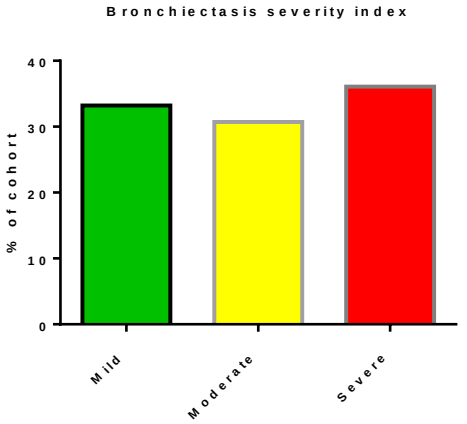

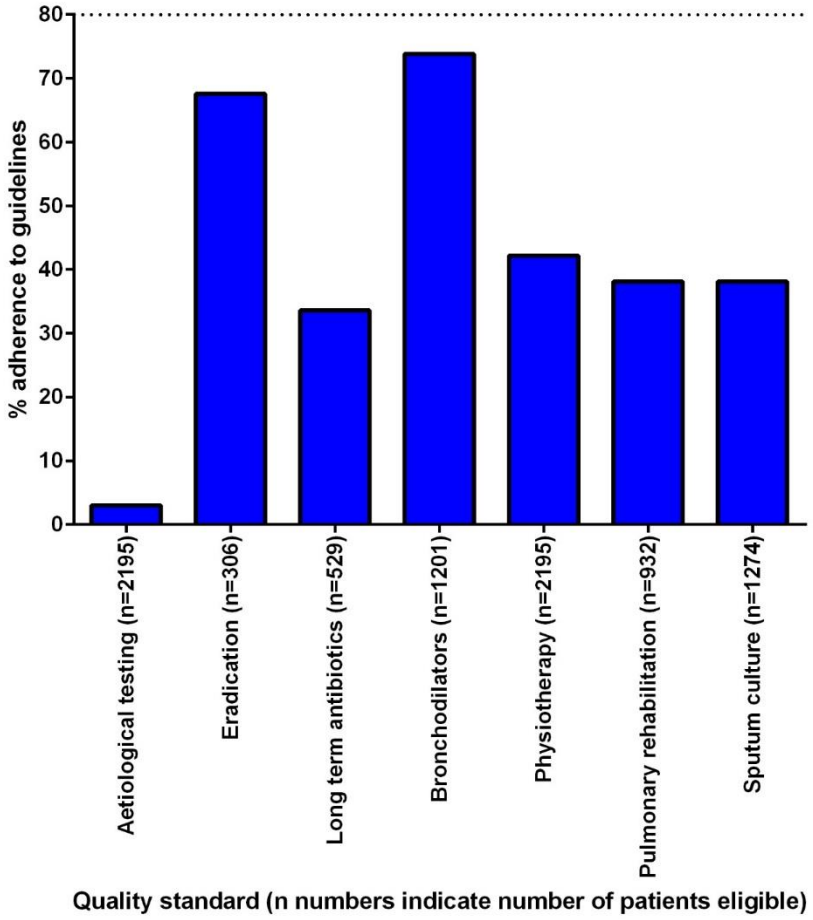

Assessment based on British Thoracic Society quality standards

80% adherence regarded as good quality care

Excludes patients where the recommendation does not apply.

WP5 objectives: EU wide registry for bronchiectasis

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European Respiratory Society guidelines for the management of adult bronchiectasis

Eva Polverino[1], Pieter C. Goeminne[2,3], Melissa J. McDonnell[4,5,6], Stefano Aliberti[7], Sara E. Marshall[8], Michael R. Loebinger[9], Marlene Murris[10], Rafael Cantón[11], Antoni Torres[12], Katerina Dimakou[13], Anthony De Soyza[14,15], Adam T. Hill[16], Charles S. Haworth[17], Montserrat Vendrell[18], Felix C. Ringshausen[19], Dragan Subotic[20], Robert Wilson[9], Jordi Vilaró[21], Bjorn Stallberg[22], Tobias Welte[19], Gernot Rohde[23], Francesco Blasi[7], Stuart Elborn[9,24], Marta Almagro[25], Alan Timothy[25], Thomas Ruddy[25], Thomy Tonia[26], David Rigau[27] and James D. Chalmers[28]

@ERSpublications
The publication of the first ERS guidelines for bronchiectasis http://ow.ly/wQSO30dU0nE

Cite this article as: Polverino E, Goeminne PC, McDonnell MJ, *et al*. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J* 2017; 0: 1700629 [https://doi.org/10.1183/13993003.00629-2017].

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 D. Chalmers[1], Felix C. Ringshausen[2], Bridget Harris[3], J. Stuart Elborn[4], Annette Posthumus[3], Charles S. Haworth[5], Nicola Pilkington[3], Eva Polverino[6], Thomas Ruddy[3], Stefano Aliberti[7], Pieter C. Goeminne[8], Craig Winstanley[9] and Anthony De Soyza[10,11]

Affiliations: [1]Scottish Centre for Respiratory Research, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK. [2]Dept of Respiratory Medicine, Hannover Medical School, Member of the German Centre for Lung Research, Hannover, Germany. [3]European Lung Foundation (ELF)/EMBARC bronchiectasis patient advisory group. [4]Host Defence Unit, Royal Brompton Hospital, Imperial College, London, UK. [5]Cambridge Centre for Lung Infection, Papworth Hospital, Cambridge, UK. [6]Servei de Pneumologia, Hospital Universitari Vall d'Hebron (HUVH), Institut de Recerca Vall d'Hebron (VHIR), Barcelona, Spain. [7]Dept of Pathophysiology and Transplantation, Università degli Studi di Milano, Internal Medicine Department, Respiratory Unit and Adult Cystic Fibrosis Center Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy. [8]Dept of Respiratory Medicine, AZ Nikolaas, Sint-Niklaas, Belgium. [9]Institute of Infection and Global Health, University of Liverpool, Liverpool, UK. [10]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK. [11]Bronchiectasis Service, Freeman Hospital, Newcastle upon Tyne, UK.

Correspondence: James D. Chalmers, Division of Molecular and Clinical Medicine, University of Dundee, Dundee, DD1 9SY, UK. E-mail: jchalmers@dundee.ac.uk

@ERSpublications
Risks of cross-infection in bronchiectasis are small, and should not currently restrict access to specialised care http://ow.ly/dkVl30hcu5p

Cite this article as: Chalmers JD, Ringshausen FC, Harris B, *et al*. 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. *Eur Respir J* 2018; 51: 1701937 [https://doi.org/10.1183/13993003.01937-2017].

Received: Sept 23 2017 | Accepted after revision: Nov 13 2017

support from the EU/EFPIA Innovative Medicines Initiative Joint Undertaking iABC grant agreement number 115721.

for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

Clinical practice guidance and consensus statements produced from EMBARC

Registry data used to underpin evidence review

Further projects planned focussing on clinical trial design

WP5 objectives: EU wide registry for bronchiectasis

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inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis

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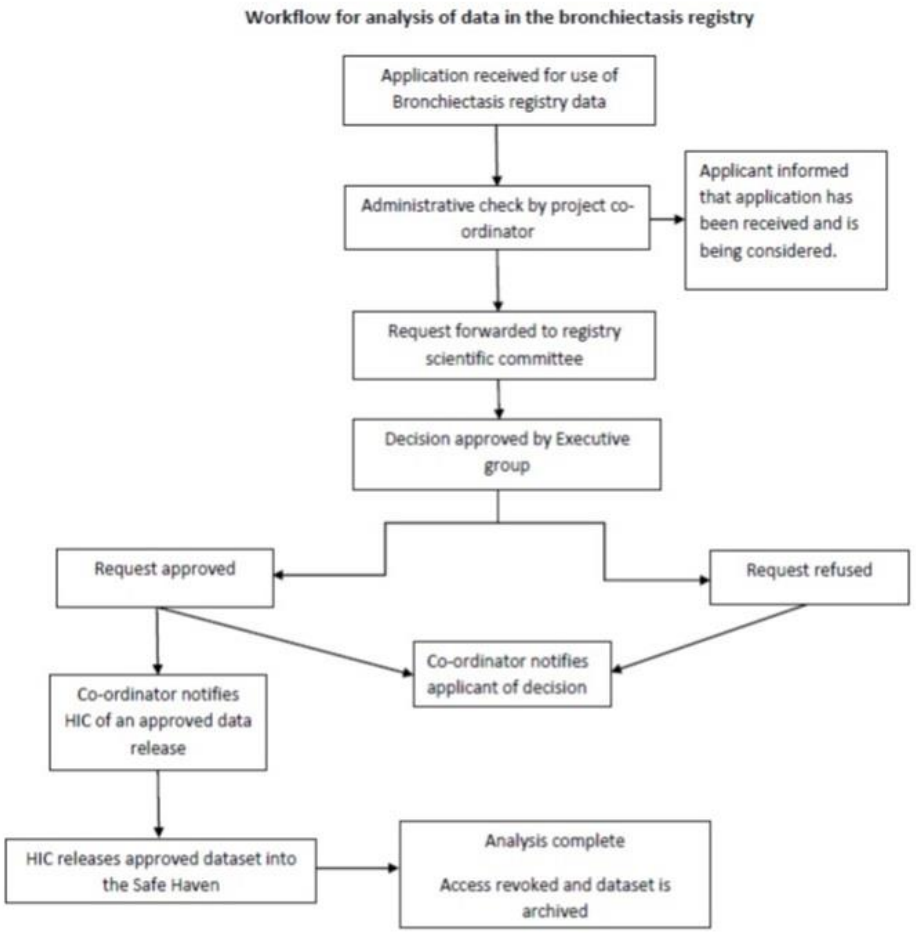
Data access is <u>open</u> following European CF registry/EMBARC principals

- Priority areas identified based on “roadmap”
- Data should be made available to any scientifically valid question
- Likely to result in a large number of peer reviewed publications
- Data access policy is published on the website.



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Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research

Adam T. Hill[1,26], Charles S. Haworth[2,26], Stefano Aliberti[3], Alan Barker[4], Francesco Blasi[3], Wim Boersma[5], James D. Chalmers[6], Anthony De Soyza[7], Katerina Dimakou[8], J. Stuart Elborn[9], Charles Feldman[10], Patrick Flume[11], Pieter C. Goeminne[12,13], Michael R. Loebinger[14], Rosario Menendez[15], Lucy Morgan[16], Marlene Murris[17], Eva Polverino[18], Alexandra Quittner[19], Felix C. Ringshausen[20], Gregory Tino[21], Antoni Torres[18], Montserrat Vendrell[22], Tobias Welte[20], Rob Wilson[14], Conroy Wong[23], Anne O'Donnell[24,27] and Timothy Aksamit[25,27] for the EMBARC/BRR definitions working group

1. World bronchiectasis congress:
   - Hannover 2016
   - Milan 2017
   - Washington 2018
2. 7th Portuguese Bronchiectasis Meeting
3. ERS Annual Congress (since 2015)
   - 4 EMBARC symposia

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click for updates

STUDY PROTOCOL
BRONCHIECTASIS

The EMBARC European Bronchiectasis Registry: protocol for an international observational study

James D. Chalmers[1,33], Stefano Aliberti[2,33], Eva Polverino[3,33], Montserrat Vendrell[4], Megan Crichton[1], Michael Loebinger[5], Katerina Dimakou[6], Ian Clifton[7], Menno van der Eerden[8], Gernot Rohde[9], Marlene Murris-Espin[10], Sarah Masefield[11], Eleanor Gerada[12], Michal Shteinberg[13], Felix Ringshausen[14], Charles Haworth[15], Wim Boersma[16], Jessica Rademacher[14], Adam T. Hill[17], Timothy Aksamit[18], Anne O'Donnell[19], Lucy Morgan[20], Branislava Milenkovic[21,22], Leandro Tramma[1], Joao Neves[23], Rosario Menendez[24], Perluigi Paggiaro[25], Victor Botnaru[26], Sabina Skrgat[27], Robert Wilson[5], Pieter Goeminne[28], Anthony De Soyza[29,30], Tobias Welte[14], Antoni Torres[3], J. Stuart Elborn[31] and Francesco Blasi[32], on behalf of EMBARC.

WP5 objectives: EU wide registry for bronchiectasis

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Sustainability- EMBARC2

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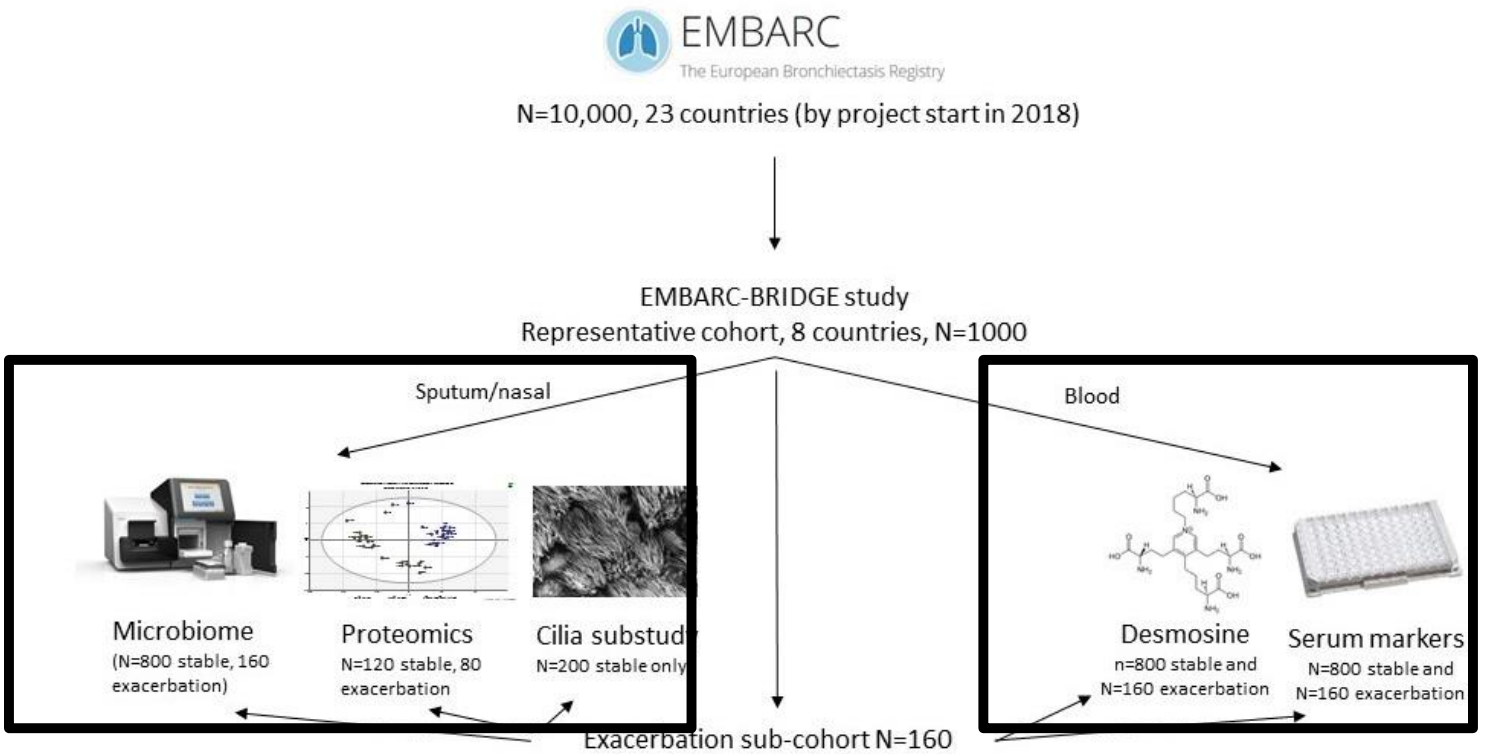
- New external funding confirmed 2018
- €1.5m from the ERS research agency and other funders
- 2019-2021

EMBARC 2

iABC
inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis



Bioinformatic analysis
- Stable endotypes
- Exacerbation endotypes

→

Internal validity
- ELISA/western blot
- qPCR, standard microbiology
- Bronchoscopic substudy (N=30)

→

External validity

WP5 objectives: EU wide registry for bronchiectasis

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inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis

Summary of achievements

- All milestones and deliverables achieved at the “half-way” stage of the project
- More than 10,000 patients enrolled into the largest bronchiectasis study ever conducted
- Over 20 publications and presentations to date
- Registry software now used by multiple bronchiectasis registries worldwide as well as paediatric asthma and chronic cough registries
- Registry now being used as the foundation for translational research and new clinical trials
- The registry has made a major contribution and will be a key legacy of the iABC project

iABC
inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis

Work Package 4

Prof Francesco Blasi

University of Milan

&

Dr Gerhild Angyalosi

Novartis

WP4 objectives: Clinical studies in patients with Bronchiectasis (BE)

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Original Scope: support the clinical development of tobramycin inhalation powder (TIP) in BE patients with a history of exacerbations and chronic Pa infection.

- Three studies were planned: a Phase II dose finding study followed by a Phase III registration program (consisting of two identical phase III studies).

Scientific gains anticipated:

- Determining the optimal dose and treatment regimen of TIP in a Phase II dose finding study
- Determining the efficacy and safety of TIP in BE patients with the aim to seek approval by regulators (currently there are no approved inhaled antibiotics in BE)
- Development of new clinically relevant endpoints (microbiome analysis, LCI and CT imaging)
- Biorepositories of clinical BE respiratory isolates and sputum samples linked to a database including microbial and patient information (WP6)
- Strengthening of EMBARC, ECFS-CTN through shared learning and expertise to develop a European BE-CTN
- Development of BE research capacity in Europe: the legacy of this project will include provision of a biorepository of sputum, blood and clinical isolates for translational research and the EU-wide BE registry which together provide a platform for the development of the European BE-CTN

WP4B: Status update on the iBEST-1 study

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iBEST-1 iABC Bronchiectasis Efficacy Study with TIP (tobramycin inhalation powder)

Dose-finding Study to Assess the Efficacy, Safety and Tolerability of Tobramycin Inhalation Powder in Patients With Non-Cystic Fibrosis Bronchiectasis and Pulmonary *P. aeruginosa* Infection

ClinicalTrials.gov Identifier: NCT02712983

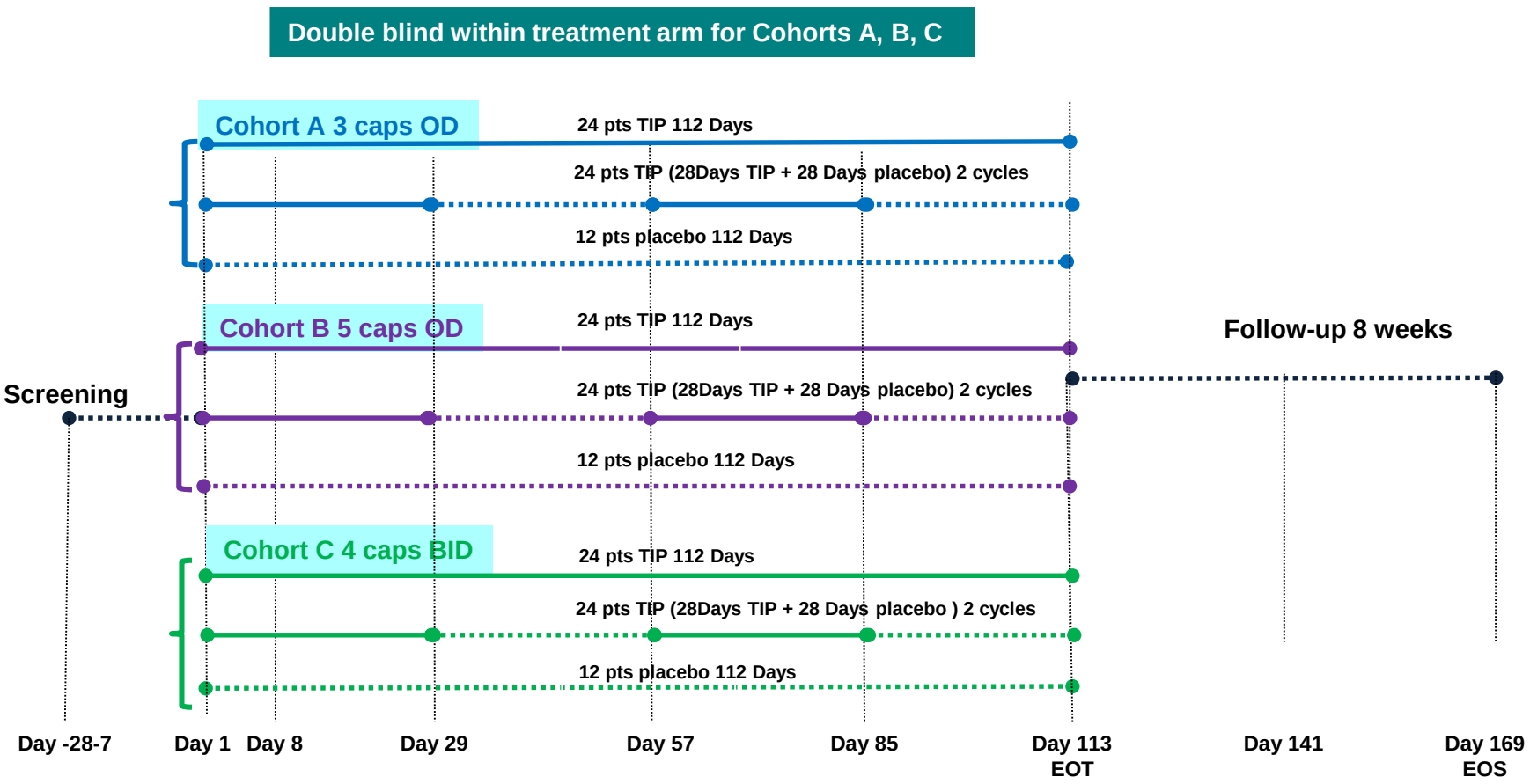
iBEST-1 Study Overview

iABC
inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis

Purpose and rationale	The purpose of this study is to support the selection of a safe and tolerable TIP dose, and regimen that exhibits effective bacterial reduction of P. aeruginosa in non-cystic fibrosis bronchiectasis (BE) patients.
Study treatment	• Tobramycin inhalation powder (TIP) drug-device combination product consisting of tobramycin dry powder for inhalation in capsules (TBM100 28 mg inhalation powder hard capsule) administered by the T-326 Inhaler. • Matching placebo capsules to TIP administered by the T-326 Inhaler.
Study design	• Blinded, randomized, dose- and regimen finding trial utilizing a 3 treatment cohort design
Population	Planned: 180 male and female BE patients ≥18 years old
Duration	196 days (28 days screening + 112 days DB treatment + 56 days follow-up

iBEST-1 CTBM100G2202 Study Design

3 cohorts 9 arms: continuous and cyclical therapy in each of the cohorts vs placebo



- **Sample size:** planned 180 patients
- **Randomization:** between cohorts: **A:B:C 1:1:1,**
  - **within cohorts A, B and C** **TIP continuous : TIP/Placebo alternating : placebo = 2:2:1**

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iBEST-1 Study Status

Recruitment as of 20 Nov 2018

- Screened: 188 Patients
- Randomized: 107 Patients (59% of the targeted 180)
- Ongoing: 13 Patients

- 7 countries, 48 sites of which 8 iABC partner sites (QUB, Univ. Milan, Papworth Hospital, Royal Brompton, Univ. Dundee, Univ. Edinburgh, VHIR, MHH); 3 iABC partners novel endpoints (QUB, EMC, UZA)

WP4 Achievements to date

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iBEST-1 study:

- 2015: study design revised based on EMA/FDA regulatory feedbacks (sample size increased 144 to 180 patients), protocol finalization
- 2016: public tender selection of CRO, study start-up activities, study supply
- 2017: 48 sites initiated in 7 EU countries
- 2018: Protocol amendment to enhance recruitment; DMC had no safety concerns, recommendation to continue study with no changes

Phase III plan:

- 2018: Trial Steering Committee (TSC) has revisited the risks on phase III plan, in light of recent regulatory advise on inhaled antibiotics in bronchiectasis (two programs in BE have received negative response letters from FDA)

iBEST-1 Lessons learned & challenges

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Challenges in execution (impacting recruitment):

- Complex study with recruitment significantly behind target (timelines have been extended several times)
  - Significant proportion of eligible patients already being treated in line with the ERS guidelines (of 48 sites initiated, only 36 have recruited patients)
  - Screen-failure rates higher than anticipated (45% vs 31% estimated) mainly due to Pa detection locally, safety exclusion criteria (renal values, impaired hearing);
  - Several sites exhausted their pool of eligible patients (Pa presence or lack of pulmonary exacerbation documentation)
  - Study start-up activities and engagement with sites suboptimal with ICON CRO

Mitigation plan to enhance recruitment:

- Close working relationship between project team and ICON senior management to stimulate existing sites and explore new opportunities: selection of 20 additional sites and 2 new countries
- iABC engagement including calls with TSC members, facilitate best practice sharing of successful sites
- Substantial amendment of the protocol released 09th Feb 2018 to facilitate recruitment.

Recent changes to the project

- On 31 August 2018, the worldwide rights to 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. Novartis and WP4 TSC have worked together to inform partners and investigators.
- All patients who signed Informed Consent and entered screening, will continue through to their last scheduled visit.
- All relevant data from the study will be analyzed and shared as per iABC publication plan and Novartis data disclosure policy.
- All WP4 & WP6 milestones and deliverables related to Phase-III have been terminated.

iBEST-1 Study timelines

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Key Milestones	Actual	Planned
Final Protocol	24 Nov 2015	
CRO start date	10 May 2016	
First patient first visit	02 Feb 2017	
Data monitoring committee meeting	21 Aug 2018	
Last patient enrolled	02 Oct 2018	
Last patient last visit		20 Mar 2019
Last data generated		Jun 2019 (tbc)
Data base lock		Jun/Jul 2019 (tbc)
Clinical study report (CSR) completion		Q4 2019 (tbc)
CSR submission to Health authorities (EU)		Mar 2020 (LPLV*+12M)

* LPLV - Last patient last visit

WP4/WP6: iABC academic partner contribution to study objectives

Study objectives	Objectives	iABC partner
Change in *P.aeruginosa* colony forming units (CFUs) from baseline to Day 29 of treatment, each compared to placebo.	Primary efficacy	Univ. Antwerp
Change in *P. aeruginosa* CFU in sputum from baseline to each post-baseline treatment visit and during the follow-up visits	Secondary	Univ. Antwerp
Change in the minimum inhibitory concentration (MIC) of tobramycin for *P. aeruginosa*.	Exploratory	Univ. Antwerp
Rate of emergence of new bacterial pathogens	Exploratory	Univ. Antwerp
Proportion of patients with negative sputum cultures for *P. aeruginosa.*	Exploratory	Univ. Antwerp
Airways inflammation markers in sputum and serum/plasma	Exploratory	Queens Univ. Belfast / ICON
Lung clearance index	Exploratory	Queens Univ. Belfast
Change in the sputum microbiome	Independent report (WP6)	Queens Univ. Belfast
Exploratory pharmacogenetic assessments to examine individual genetic variation in genes relating to the underlying disease causing bronchiectasis	Independent report (WP6)	Univ. Dundee
Development CT- scoring system for bronchiectasis	Independent report (WP6)	Univ. Rotterdam

Ongoing and planned activities

- Complete the study with high quality data, minimize missing values.
- Planning activities for data integration from various vendors and academic partners to lock database.
- Revise the statistical analytic plan to accommodate for the reduced sample size (some sensititivity analyses for primary endpoint not anymore relevant, additional analyses for secondary endpoints included, eg. pooling by cohort and by treatment regimen)
- Preparation of clinical study report activities.

WP4B: Summary current vs plan

Milestone / Deliverable	Description	Planned (DoW-original)	Planned (DoW - Amendment)	Status (Actual)
D4.1	Regulatory advice for Phase II trial of TIP in BE patients	M4 (Dec 2015)	M4 (Dec 2015)	✓ Completed (M0, Jul 2015)
M4.3	Site selection and pre-identification complete for phase II TIP study	M6 (Feb 2016)	M6 (Feb 2016)	✓ Completed (M9, Apr 2016)
M4.4	First patient first visit in Phase II trial of TIP	M9 (May 2016)	M15 (Nov 2016)	✓ Completed (M18, Feb 2017)
M4.5	Completion of enrolment in Phase II trial of TIP	M18 (Feb 2017)	M27 (Nov 2017)	✓ Completed (M38, Oct 2018)
M4.6	Completion of the Phase II TIP study (LPLV)	M24 (Aug 2017)	M33 (May 2018)	*Estimated (M43, Mar 2019)*
D4.2	Phase II trial of TIP in BE patients (abbreviated report of key outcomes)	M30 (Feb 2018)	M39 (Nov 2018)	*Estimated (M51, Dec 2019 TBC)*

Associated WP6 milestones regarding endpoint validations will also be affected

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Work Package 6

Prof Michael Tunney

Queen's University Belfast

WP6: Novel endpoints

- Sputum microbiology
- Novel endpoints

Aims

- to determine changes in sputum density and antimicrobial susceptibility of Pa and other pathogens in clinical trials
- to evaluate changes in airway microbiome composition as a novel exploratory endpoint for measuring microbiological efficacy in clinical trials in CF and BE
- to explore molecular determination of resistance genes (resistome) in response to inhaled antibiotic therapy
- to evaluate LCI as an endpoint for clinical trials in CF and BE
- to evaluate chest CT outcome measures as a novel endpoint/predictor of treatment response for clinical trials
- to evaluate if sputum inflammatory biomarkers can be used as exploratory secondary endpoints in clinical trials in CF and BE

Sputum microbiology

- Screening
  - Qualitative microbiology: presence of relevant organisms
- Clinical studies
  - Quantitative microbiology
  - Antimicrobial susceptibility testing
- Repository of clinical isolates and clinical samples

Sputum microbiology: Achievements/Key results

- Development of a standardized laboratory manual for quantitative sputum microbiology
- LAB-Net: quality assurance & training where necessary
- Sample processing : iBEST-1

iBest-1: Samples processed

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- 107 patients randomized
- 1307 samples processed
  - 1137 sputum
  - 170 swabs
- 4685 sample aliquots sent to Belfast
  - Multiple aliquots from same samples

iBest-1: Bacteria cultured

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- 614 *P. aeruginosa* isolates cultured and stored
  - Sputum (n=604) & swabs (n=10)
- 116 additional BE pathogens cultured and stored (n=58 patients)
  - *S. aureus*, n=55
  - *A. xylosoxidans*, n=22
  - *H. influenzae,* n=14
  - *S. maltophilia,* n=10
  - *S. pneumoniae*, n=7
  - *Klebsiella spp.*, n=4
  - *M. catarrhalis*, n=2
  - *Proteus spp.,* n=2

iBest-1: Susceptibility testing

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- 524 *P. aeruginosa* isolates
- Tobramycin & other antibiotics
- Broth microdilution according to CLSI guidelines

WP6: Novel endpoints

Exploratory endpoint	Regulatory endpoint	Clinical Trials	WP
Lung Clearance Index (LCI)	FEV_1	• TIP Phase II dose finding study: BE • TIP Phase III efficacy /safety studies: BE (in EU) • POL7080 Phase IB PK/Safety and POC study in CF	4B 4B 8
Computed tomography (CT) scanning	FEV_1	• TIP Phase II dose finding study: BE • TIP Phase III efficacy /safety studies: BE	4B 4B
Microbiome analysis Resistome analysis	Bacterial load (cfu/g sputum) Resistance development (MIC)	• TIP Phase II dose finding study: BE • TIP Phase III efficacy /safety studies: BE • POL7080 Phase IB PK/Safety and POC study in CF	4B 4B 8

WP6: Novel endpoints

Exploratory endpoint	Regulatory endpoint	Clinical Trials	WP
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LCI: Achievements/Key results

- 25 LCI devices purchased
- 19 new devices distributed to sites participating in LCI sub-study (iBEST-1)
- 8 sites with existing devices participating in LCI sub-study

LCI: Achievements/Key results

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- Training programme and eLearning tool developed
- Training delivered to 20 sites
  - Certification: n=13/20
  - Certification ongoing: n=5/20
  - Withdrawn: n=1
- Central LCI reading service set up and functional
  - LCI data from 37 patients across 10 sites received
  - 69% of LCI tests met quality criteria

CT scanning: Achievements/Key results

- Development of website for standardization of chest CTs
  - Website developed and currently being tested
  - Pilot phase: Q4 2018
- Scoring baseline CTs
  - 61 complete CT scans received from patients in iBEST-1
  - Scoring will commence once all scans received

Microbiome analysis: Achievements/Key results

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- Standardized protocols developed for
  - DNA extraction
  - qPCR
  - Next-generation sequencing (Illumina MiSeq platform)
- qPCR vs. quantitative culture compared in excess sputum samples
  - *P. aeruginosa*

Microbiome analysis: iBEST-1

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- 468 samples received by microbiome lab
  - 398 sputum
  - 70 swabs
- 227 samples processed
  - all sputum
  - Currently adapting protocol for DNA extraction from swabs
- 78 samples sequenced
  - Data analysed but not linked with patient identifiers

WP6: Sputum inflammatory biomarkers

Exploratory endpoint	Comparison with:	Clinical Trials	WP
Neutrophil elastase,calprotectin, cytokines (e.g. IL-8, IL-6, TNFα, IFNg, IL-1β)	Conventional culture endpoints Exploratory microbiological, LCI and CT endpoints	• TIP Phase II dose finding study: BE • POL7080 Phase IB PK/Safety and POC study in CF	4B 8

Analysis to be completed once all samples collected

Issues/concerns

- iBEST-1
  - Reduced sample size for analysis of exploratory endpoints
  - No phase III study to test endpoints in larger number of patients
- LCI
  - High % of tests (31%) excluded as they did not meet the quality criteria
  - Small sample size in iBEST-1 sub-study
- Website for standardization of chest CT scans not functional

Future plans

- iBEST-1
  - Completion of quantitative sputum microbiology and antimicrobial susceptibilty testing
  - Completion of LCI sub-study
  - Complete development of website for standardization of chest CT scans and score available CT scans
  - Microbiome and resistome analysis
  - Inflammatory biomarker analysis
  - Comparsion of exploratory and conventional endpoints

Future plans

- POL7080 Phase IB safety and POC study in CF
  - Quantitative sputum microbiology
  - LCI study
  - Microbiome and resistome analysis
  - Comparsion of exploratory and conventional endpoints
- Research programme with new partner(s)
- Additional clinically relevant research
  - Potential role of fungi and viruses in triggering exacerbations
  - Shotgun metagenomics: development of resistance

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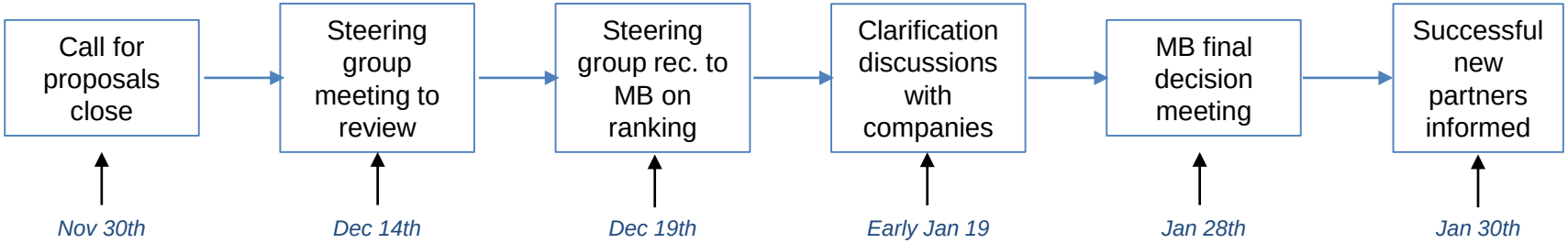
Plans and Mitigations 2019/2020

Plan 2019: Consortium change

- Call issued mid October 2018, through BEAM Alliance, EFPIA and consortium contacts
- 16 expressions of interest from companies
- Call closes Friday 30th Nov 2018



- Work with new partners will continue throughout Q1 2019 to develop the work plan and budget
- Consortium will present an amendment request to IMI at the end of March.
- Target is to bring the new partner on board officially by 01 August

WP9 New Novartis drug may improve BE outcomes by improving airway hydration and mucus clearance

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1. Increased mucus and bacterial colonization is observed in BE

- BE are associated with reduced mucociliary clearance, resulting in bacterial colonization, mucus plugging and airflow obstruction
- accelerates lung inflammation and functional decline
- increases exacerbation risk

2. There is evidence of ion channel dysfunction in patients with BE

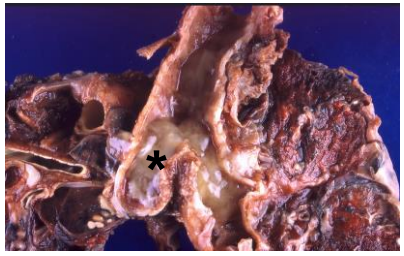
- decreased airway hydration and reduced mucus clearance
- increased bacterial colonization
- significant small airway disease, with features of goblet cell/mucus gland hyperplasia

3. NVS drug is expected to increase CFTR function in BE

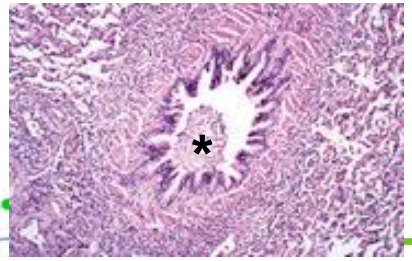
- improves mucus clearance
- reduces bacterial colonization
- as a result, may reduce pulmonary exacerbations and improve airway inflammation, airway obstruction, lung function and symptoms

Mucus plug* in large (A) and small (B) BE airway

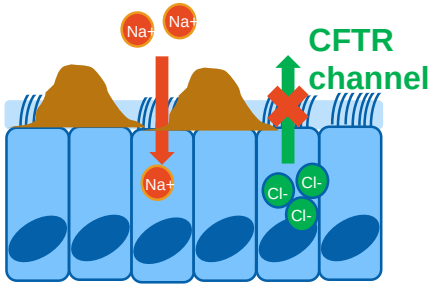
A



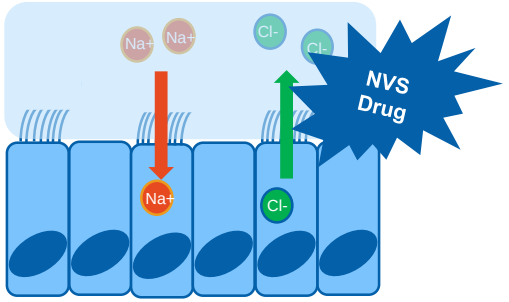
B



Decreased mucus clearance



Improved mucus clearance



WP9, Plan 2019 – Novartis proposal

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- Novartis proposes to conduct a Ph2a proof-of-concept study for a novel drug candidate that is targeting mucocilliary clearance (MCC)
  - In contrast to antibiotics, improving MCC is hypothesized to reduce bacterial colonization regardless of pathogen and without the limitation of potential development of treatment resistance
  - Evidence suggests many BE patients have a component of ion channel dysfunction, including CFTR.
  - Previous study results (not disclosed) with the proposed drug suggest improved MCC, improved lung function, reduced inflammation and infections in chronic respiratory diseases.
- Expected contribution from the iABC consortium partners
  - Strong scientific expertise to develop this novel therapy in Bronchiectasis.
  - WP4 clinical partners showed primary interest for MoA and study proposal. Proposal to continue working with WP4 partners as TSC and clinical sites.
  - Similar measurements and endpoints to be conducted by WP6 partners (microbiology, CT-scan and inflammatory biomarkers)
  - Leverage on EMBARC WP5 network for study feasibility and site identification (as previously for iBEST-1)
  - Novartis already EPFIA partner/coordinator. Consideration to execute the Ph2a study across Europe and China, within 3 years (before End of the grant) and sharing lessons-learned from previous study.

Plan 2019: iBEST1

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- LPLV: 20 Mar 2019
- Last data generated: Jun 2019 (tbc)
- Database lock: Jun/Jul 2019 (tbc)
- CSR from CRO: Q4 2019
- CSR submission to Health authorities (EU) Mar 2020 (LPLV*+12M)

* LPLV - Last patient last visit

Plan 2019: WP7

- Development of inhaled murepavadin
  - Pre-clinical toxicology
  - Preparation of clinical studies
  - Preparation of regulatory approval
  - Continue development of DPI-formulation
  - Plans to begin with of a liposomal-formulation
- Scientific
  - (Further) analysis of WGS data
  - Further development and analysis of open biofilm model
  - Further development β-ENaC mouse model (and testing murepavadin)
  - Report on breakpoint development for inhaled therapy

Plan 2020: WP8 clinical study

- Development of inhaled murepavadin
  - Regulatory approval Phase Ia
  - Phase Ia
    - PK and safety study in healthy subjects
  - Preparation regulatory approval Phase Ib

Plan 2020 – WP10 (New partner)

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We are anticipating either:

- Another pre-clinical /early stage clinical programme
- A clinical programme to re-purpose an established antibiotic for CF/BE

We have asked for

- Proposals which comply with the IMI JU 11th call Topic 7
- Partners who have a team and funding in place ready to begin work & can complete by end December 2021

If possible we would like:

- A proposal which fits with the current capabilities of the consortium
- Experience of working within an IMI/H2020 structure

Projected outcomes and benefits to patients

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- A strong consortium with the possibility of forming an ongoing alliance to continue work under future grants.
- 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
- Repositories of clinical respiratory isolates and sputum biobanks for use in future research
- Initial results on the therapeutic efficacy of TIP in BE patients
- Novel endpoints (microbiome, LCI and CT imaging) for clinical trials in both CF and BE
- An inhaled formulation and dispersion device for Murepavadin
- Data on the pharmacokinetics, safety and efficacy of POL7080 in CF patients.

To be updated Jan 2019 following discussions on new programmes

Items for discussion

- Timing will be an issue for existing WPs, but more so for the new programmes to be added this year. What are the options open if work extends beyond Dec 2021?
- Future sustainability. Opportunities in IMI 2 and IMI 3
- Brexit

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Thank you for your attention