iABC
inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis

Work Package 10
Clinical development of QBW251 for use in patients with bronchiectasis

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Novartis

QBW251 – Executive Summary

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- Bronchiectasis is a progressive disease with high unmet need and lack of evidence for many treatments
- QBW251 represents an exciting novel approach to improve disease outcomes in Bronchiectasis patients with a unique mode of action
- QBW251 study in Bronchiectasis is anticipated to start in March 2020 in Europe and June 2020 in China
- QBW251 studies in COPD are ongoing: Ph2b dose range finding study started in September 2019 (N = 900) and an additional mechanism of action study is anticipated to start in December 2019 (N = 100)

Significant unmet medical need for treatment of bronchiectasis

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- ERS 2017 guidelines[1] for the management of adult bronchiectasis highlighted the lack of evidence for many treatments of bronchiectasis
- Bronchiectasis has long been a neglected disease. The prevalence of bronchiectasis has been estimated at 53 to 566 cases per 100 000 inhabitants. Prevalence increases with age and female gender[1]
- High morbidity due to frequent exacerbations impairing quality of life, facilitating resistance to antibiotics, and leading to reduced lung function [1]
- Approximately 2-fold higher age-adjusted mortality compared to the general population [2]

[1] Polverino E et al. Eur Resp J 2017;50:1700629; [2] Quint J et al. Eur Respir J 2016;47:186-193

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CFTR and Bronchiectasis

QBW251- a Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

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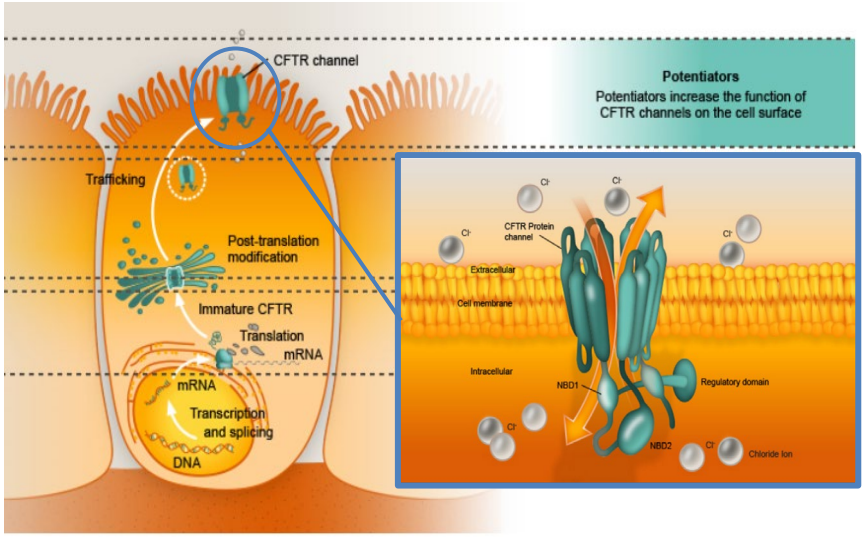
Reasons to believe in efficacy of QBW251 in Bronchiectasis

- CFTR, an epithelial chloride and bicarbonate channel supports normal airway hydration, mucus composition and mucociliary clearance and may be impaired in Bronchiectasis
- Evidence suggests many bronchiectasis patients have a component of ion channel dysfunction, including CFTR
- Molecular mechanism for reduced mucociliary clearance in Bronchiectasis may relate to dysfunction in mutated and wild-type CFTR
- Bronchiectasis shows features of goblet cell/mucus gland hyperplasia, sharing similarities with CF and COPD
- Altered and increased mucus in Bronchiectasis pts may cause airflow obstruction, accelerate LF decline, increase bacterial colonization and inflamation... leading to lung infections and exacerbations



QBW251 aims to restore CFTR function in Bonchiectasis

- improving mucus clearance
- reducing bacterial colonization
- reducing airway obstruction
- improving exacerbations, symptoms and lung function

Current therapeutic options
(beyond bronchodilators)

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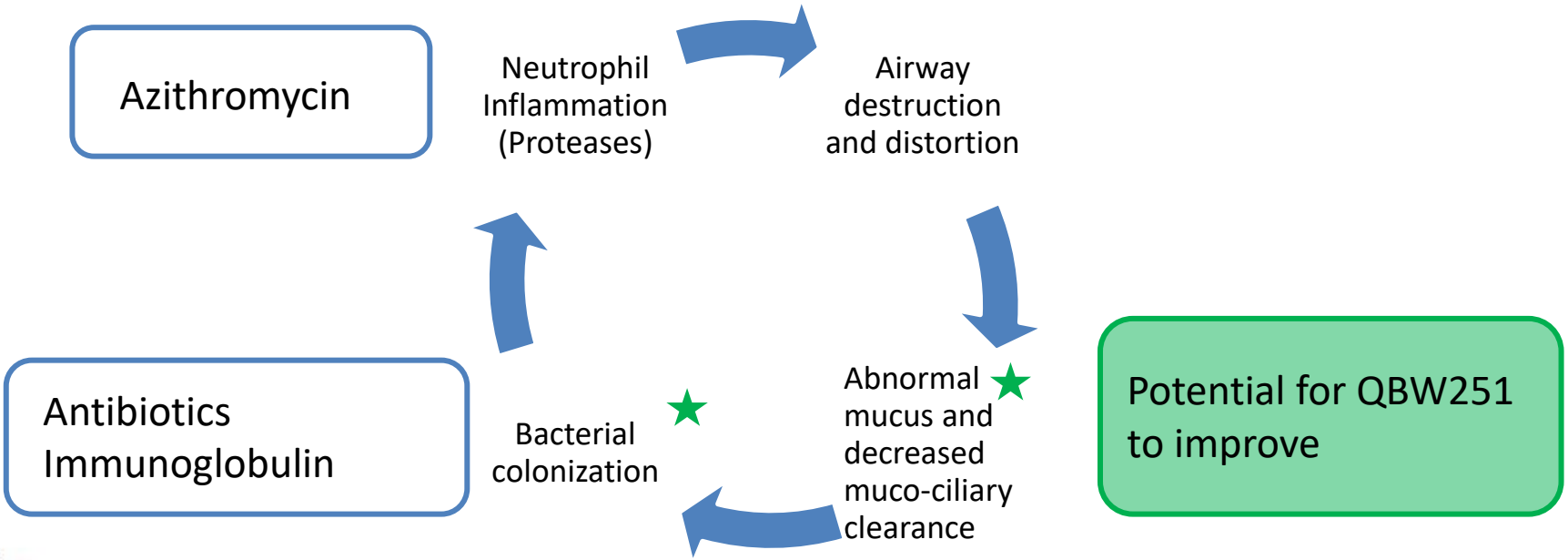
Clinical hypothesis for QBW251 in bronchiectasis:
QBW251 will improve muco-ciliary clearance (MCC) in bronchiectasis, resulting in decreased bacterial colonization, decreased small airway inflammation, improved FEV1 and ultimately fewer exacerbations



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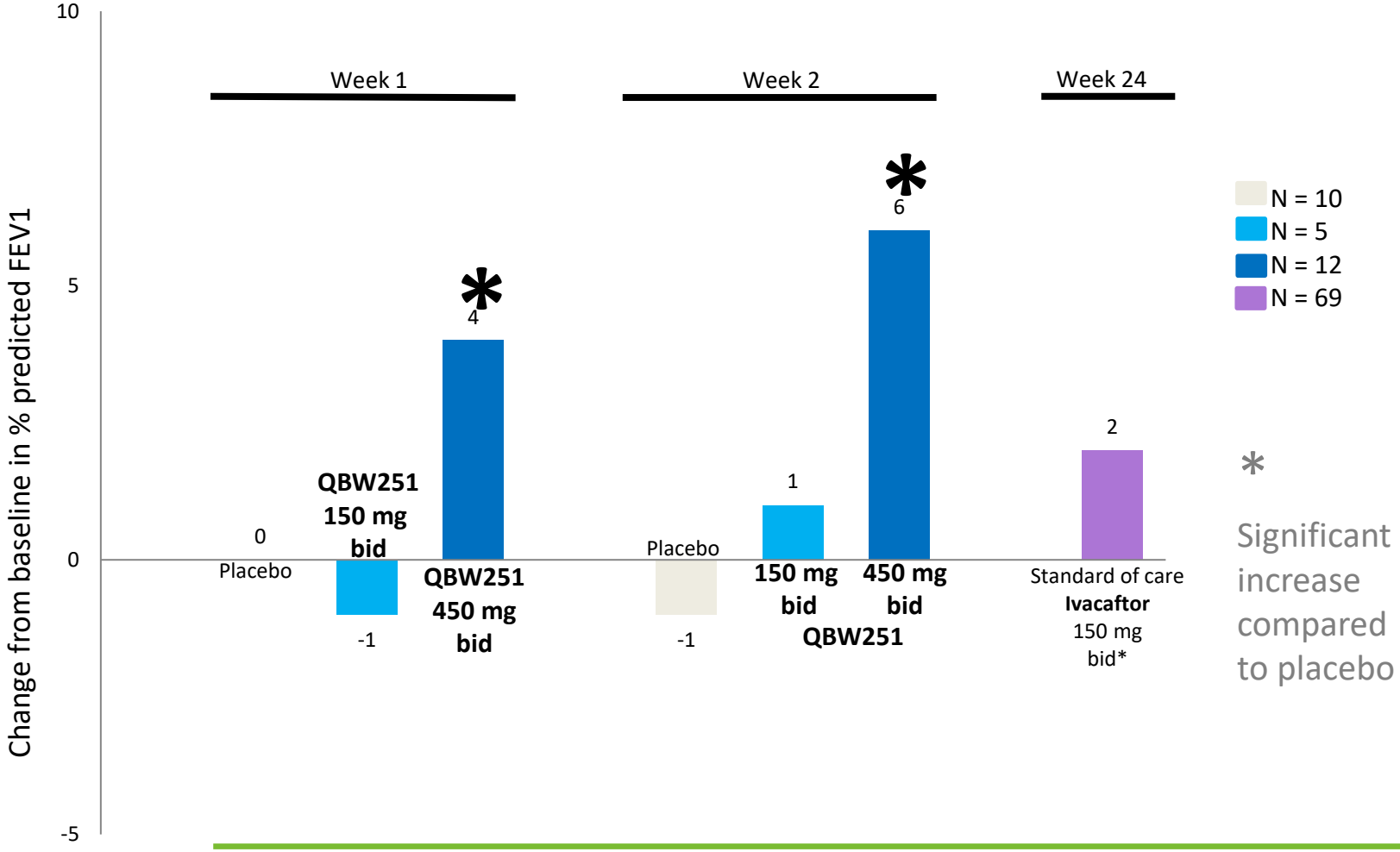
QBW251 improved lung function in Cystic fibrosis patients with gating or residual function CFTR mutations



QBW251 improved lung function in patients with COPD

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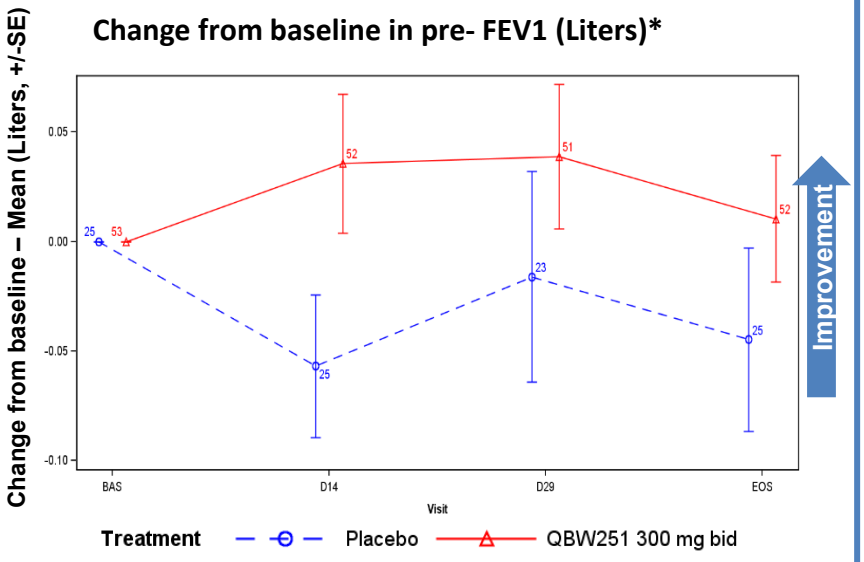
Prebronchodilator

- Pre-bronchodilator FEV1 at Day 29 showed a mean 50 mL improvement over placebo with 85% probability the effect is better than placebo

Change from baseline in pre- FEV1 (Liters)*

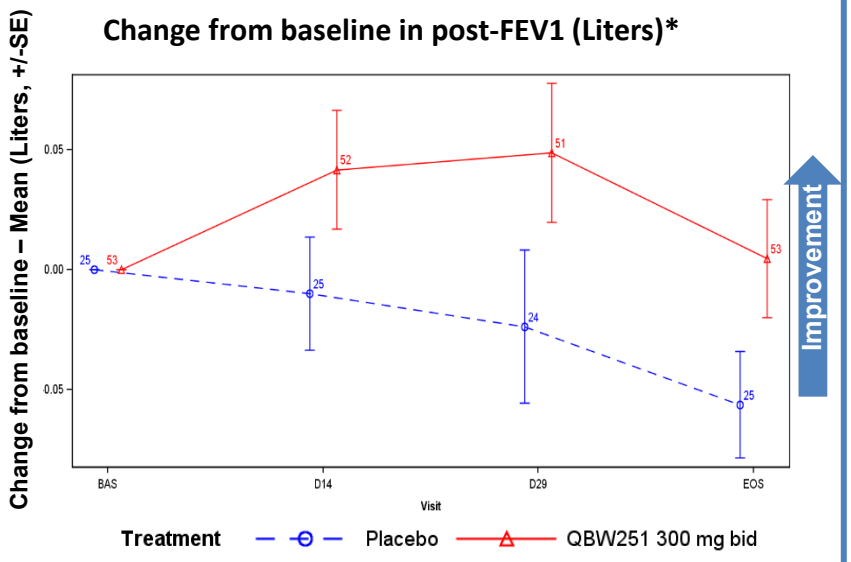


* Bayesian analysis with an informative prior

Postbronchodilator

- Post-bronchodilator FEV1 at Day 29 showed a mean 60 mL improvement over placebo with 90% probability the effect is better than placebo

Change from baseline in post-FEV1 (Liters)*



* Mixed effects analysis

Significant impact on markers of target engagement and inflammation

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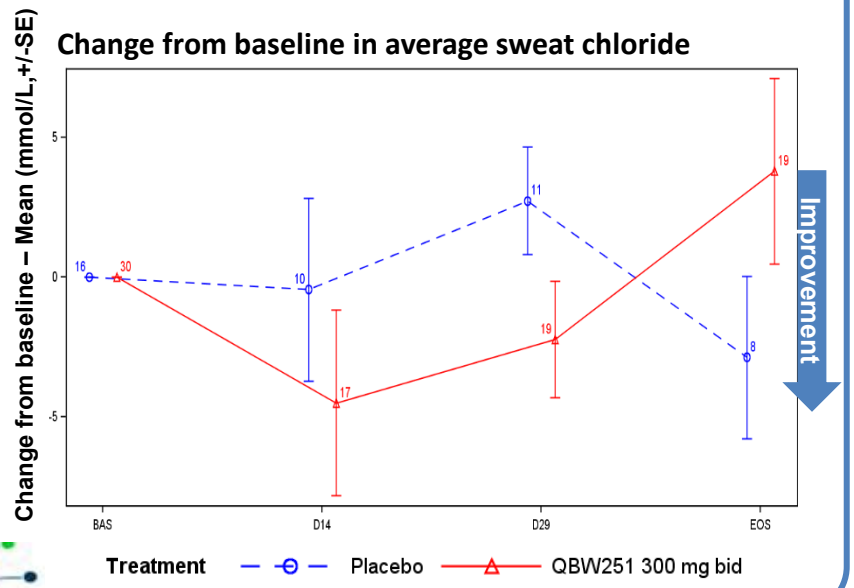
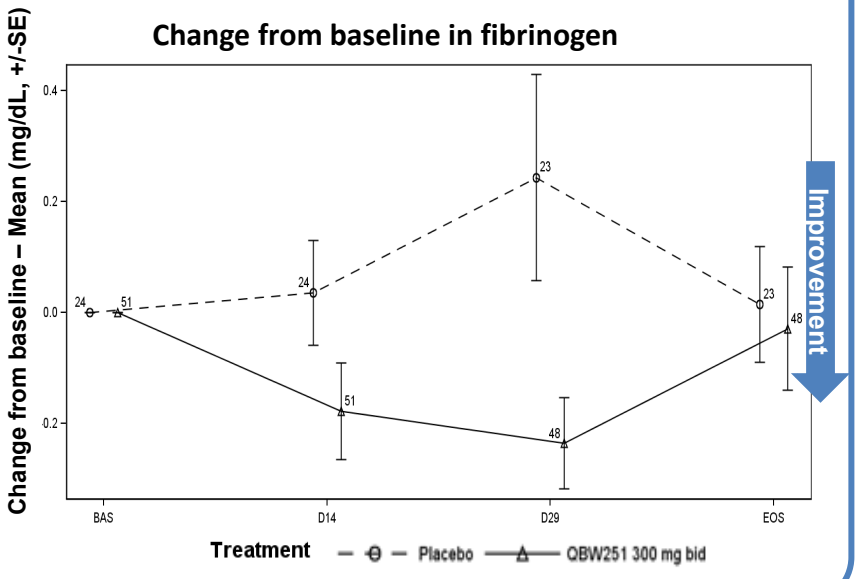
Sweat Chloride

- Statistically significant change from baseline in sweat chloride (5.19 mmol/L decrease) suggests expected target engagement (p-value = 0.091)
- Baseline sweat chloride levels = 23 mmol/L
- NB small sample sizes (~40%-60% of subjects with adequate samples at different timepoints)



Fibrinogen

- Systemic inflammation (IL-6, CRP, fibrinogen) associated with worse clinical outcomes in COPD, and fibrinogen is approved prognostic biomarker by FDA
- Baseline fibrinogen levels = 320 mg/dL
- Statistically significant change from baseline in fibrinogen (40 mg/dL decrease) supports indirect anti-inflammatory effect for mechanism of action (p-value = 0.006)



WP10 – Study overview

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- CFTR potentiator QBW251: small molecule, represents a novel mechanism of action
- QBW251C12201: Proof of concept study in patients with bronchiectasis
  - Randomized, double blind, placebo-controlled, parallel design
  - Primary objective: changes from baseline of sputum bacteria colonization
  - Secondary objectives: lung function, fibrinogen,rescue medication use, pharmacokinetics, Safety and Tolerability
  - 72 patients will be randomized to QBW251 or placebo arm with ratio of 1:1
  - QBW251: 450mg b.i.d /placebo for 12 weeks
  - Co founded by Innovative Medicines Initiative(IMI) and Novartis will be executed as part of the iABC project
  - Countries and sites: United Kingdom(5), Germany(3), Italy(1), Spain(2), China(4) , European sites will be managed by Contract Research Organisation hired by iABC. Regulatory, drug supply and over study management are with Novartis

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Suggested sites-15 sites
--- 0.8 pt/site/month

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- *EU sites : 11 to contribute 54 patients*
  - *iABC consortium partnership sites (8 sites)*

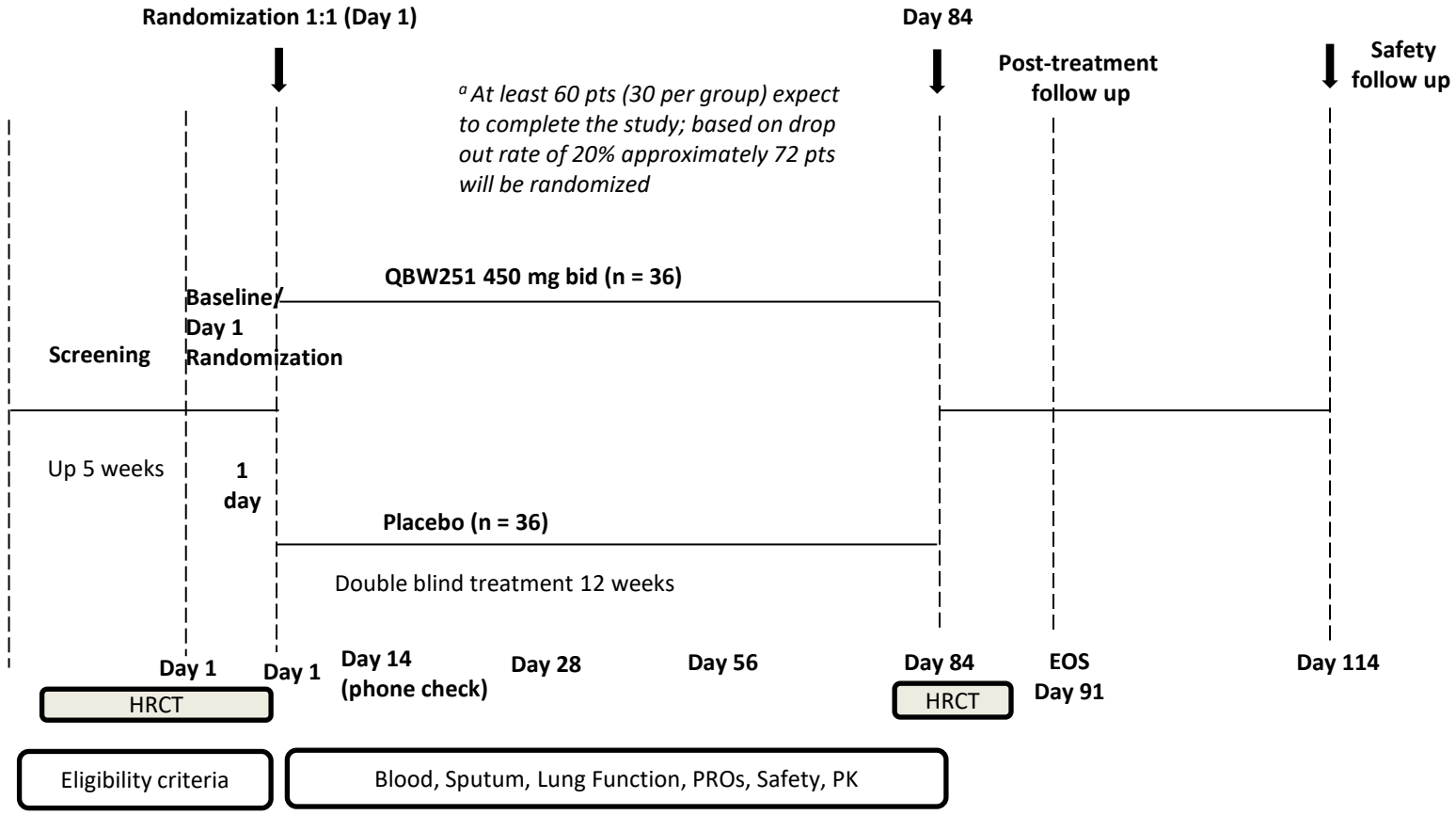
UK	Belfast Health and Social Care Trust (BHSCT Clinical site)
UK	University of Edinburgh (UNEDIN/NHS Lothian clinical site)
UK	Royal Brompton Hospital (RBHT Clinical site)
UK	Papworth Hospital (PAP Clinical site)
UK	University of Dundee (UNIVDUN/NHS Tayside clinical site)
Italy	University of Milan (UMIL/iRCCS Clinical site)
Germany	Medizinische Hochschule Hannover (MHH Clinical site)
Spain	Vall d'Hebron University Hospital (VAL clinical site)

  - *The other 3 sites recommended by TSC (3 sites)*

Spain	Hospital de la Santa Creu i Sant Pau Barcelona
Germany	PRI Grosshansdorf Henrik Watz
Germany	IKF Pneumologie Frankfurt Marc Oliver Kornmann

CN sites will come from China BE collaboration network(3-4 sites), contributing 18 pts

WP10 – Bronchiectasis study design flow chart



HRCT: High Resolution Computerized Tomography
PROs: Patient Reported Outcomes

WP10 – Laboratories ---Sputum Lab assessment

- Primary endpoint assessment: microbiology lab in University Hospital of Antwerp (UZA)
  - Sputum bacterial colonization measurement(CFU/mL): quantitative measurement of CFU: at least one of the potentially pathogenic microorganisms: *H. Influenzae, M catarrhalis, S aureus, S pneumoniae, Enterobacteriaceae, P aeruginosa, Stenotrophomonous maltophilia*
- Exploratory endpoints assessment: lab in Queens University Belfast (QUB):
  - Sputum inflammatory biomarkers: include but not limited to IL-6, IL-8 and mucin
  - Sputum bacterial load assessment measured by 16S rRNA PCR
  - Sputum bacteria species profile measured by 16S rRNA gene sequencing

WP10 – study timeline

- Key Milestones and timelines (5 countries, 15 sites, recruitment rate 0.8 p/site/month)

Milestones	timeline
IMI agreement/endorsement	**19-Sep-2019**
Protocol finalization	26-Oct-2019
First patient first visit (FPFV) (site in EU, 11 sites)	11-Mar-2020
First patient first visit (FPFV) (sites in China,4 sites)	11-Jun-2020
1st IA (14 pts completing Day 84)	Feb-2021
Last patient first visit (LPFV)	11-Apr-2021
Last patient last visit (LPLV)	03-Sep-2021
Data base (cDB) lock	29-Oct-2021
First interpretable results (FIR)	12-Nov-2021
Clinical study report (CSR) publishing	05-Mar-2022

Back-up

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WP10 –Primary/Secondary objectives

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- Primary objective/endpoint:
  - To assess the change on sputum bacterial colonization
    - Change from baseline in bacterial load of colony forming units (CFU/mL) of potentially pathogenic microorganisms in spontaneous sputum with QBW251 compared to placebo
- Secondary objectives/endpoints
  - To assess the change of QBW251 compared to placebo on sputum bacterial clearance
    - Proportion of patients with absence of any CFU of potentially pathogenic bacteria in sputum culture
  - To assess the change on patient reported outcome (PRO)
    - Changes from baseline in quality of life QOL-B (respiratory symptoms domain)
  - To assess the change of fibrinogen plasma concentration
    - Change from baseline in fibrinogen plasma concentration
  - To assess the change of lung function
    - Changes from baseline in pre- and post-bronchodilator FEV1, FVC
  - To assess the pharmacokinetics of QBW251 in patients with bronchiectasis
  - To assess the safety and tolerability of QBW251 in patients with bronchiectasis

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WP10 –Exploratory objectives

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- To assess the change on sputum bacterial colonization
  - Change from baseline in sputum bacterial colonization measured by 16S rRNA PCR
- To assess the change of QBW251 compared to placebo on sputum bacterial clearance
  - Proportion of patients with absence of any CFU of potentially pathogenic bacteria in sputum culture
- To assesse the change on patient reported outcome (PROs)
  - Changes from baseline in Bronchiectasis health questionnaire (BHQ)
  - St George's Respiratory Questionnaire (SGRQ)
  - Euro Quality of Life-5 Dimensions-3 level (EQ-5D-3L)
- To assess the change in airway structure and function
  - Change from baseline in airway wall and lumen parameters along with extent of global and regional air trapping as measured by High-resolution computerized tomography (HRCT)
- To assess the effect on mucus burden
  - Changes from baseline in whole lung and regional assessment of HRCT endpoints for distribution of mucus
- To assess the effect on exacerbations
  - Time to first event and annualized rate of exacerbations
- To assess the change on biomarkers of inflammation
  - Changes from baseline in blood and sputum e.g. inflammatory proteins, hsCRP, neutrophils, eosinophils

WP10 –Inclusion Criteria

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- Male or female patients aged ≥18 years at screening.
- Proven diagnosis of bronchiectasis by chest HRCT
- Evidence of sputum bacterial load of ≥10^6 CFU/mL with at least one potentially pathogenic microorganism (*H. Influenzae, M catarrhalis, S aureus, S pneumoniae, Enterobacteriaceae, P aeruginosa, Stenotrophomonous maltophilia. Any organism that is to be included that is not included in the list above requires approval by the steering committee/sponsor.*
- Documented history of at least one bronchiectasis exacerbation in the 12 months prior to screening.
- Patients with bronchial hypersecretion, defined as productive cough that occurs on most days (defined as >50% days) for at least three consecutive months within 12 months prior to screening, as assessed by medical history.

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WP10 –Exclusion Criteria

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- Patients who have a clinically significant ECG abnormality before randomization
- Patients requiring long-term oxygen therapy for chronic hypoxemia.
- Patients with bronchiectasis who have had a pulmonary exacerbation 4 weeks before screening
- Hemoptysis, requiring medical intervention at any time within 4 weeks prior to screening.
- Bronchiectasis predominantly characterized by isolated cavitary lung lesions.
- Patients with bronchiectasis requiring therapy that may interfere with the assessment of QBW251 efficiency or that are unlikely to respond to QBW251
- Current or ex-smokers with a minimum of 10 pack years with severe emphysema
- Patients with another concomitant pulmonary disease according to the definition of the International ERS/ATS guidelines, ie COPD, asthma, interstitial pulmonary fibrosis (IPF), sarcoidosis or other granulomatous or infectious process. Concomitant COPD and asthma with characteristics of airway hyperresponsiveness as well as COPD-Asthma overlap syndrome are allowed as long as it is not the main, primary diagnosis.
- Patients currently receiving treatment for nontuberculous mycobacterial (NTM) pulmonary disease.
- Patients receiving any medication that may influence the response to treatment within 4 weeks prior to screening eg systemic immunomodulators, mucolytics or hyperosmolar agents, recombinant human DNAse, any systemic or inhaled antibiotics (macrolides are allowed if given 3 months before screening in a stable dose)
- Patients with a body mass index (BMI) of more than 40 kg/m2