FORMAT A1 SAP	Statistical Analysis Plan for Appendix A1
Version 1.0	

Statistical Analysis Plan

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LIST OF ABBREVIATIONS

AE	Adverse Event
AI	Adaptive Intervention
ATS	American Thoracic Society
BAL	Bronchoalveolar Lavage
BAR	Bayesian Adaptive Randomisation
BCM	Biased Coin Minimisation
BP	Blood Pressure
CF	Cystic Fibrosis
CI	Chief Investigator
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
FOR*Ma*T	Finding the Optimal Regimen for *Mycobacterium abscessus* Treatment
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HREC	Human Research Ethics Committee
IA	Inhaled Amikacin
ICH-GCP	International Council for Harmonisation Good Clinical Practice Guidelines
iDSMB	Independent Data Safety Monitoring Board
ITT	Intent-To-Treat
IV	Intravenous
IVA	Intravenous Amikacin
LOCF	Last Observation Carry Forward
MABS	*Mycobacterium abscessus*
MABS-PD	MABS Pulmonary Disease
MBS	Medicare Benefits Scheme
MCRI	Murdoch Children's Research Institute
MedDRA	Medical Dictionary for Regulatory Activities
NTM	Non-Tuberculous Mycobacteria
PBS	Pharmaceutical Benefits Scheme
PI	Principal Investigator
PICF	Participant Information and Consent Form
QA	Quality Assurance
QoL	Quality of Life
RCT	Randomised Control Trial
REDCap	Research Electronic Data Capture
SAEs	Serious Adverse Events
SD	Standard Deviation
SE	Standard Error
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TDM	Therapeutic Drug Monitoring
TMC	Trial Management Committee

TSC	Trial Steering Committee
WHO DD	World Health Organization Drug Dictionary

1. ADIMINISTRATIVE INFORMATION

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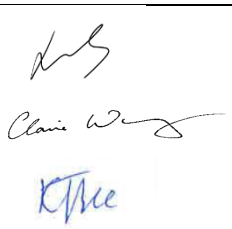
1.1. DOCUMENT VERSION HISTORY

Version Date	Version	Author/s	Signature/s	Change Description	Reason/Comment
28/04/2026	1.0	Xiaofang Wang, Katherine Lee, James Wason		Initial release.	Not applicable.

1.2. APPROVALS

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and confirm that this analysis plan was developed in a completely blinded manner (i.e. without knowledge of the effect of the intervention being assessed)

Name	Role on Study	Affiliation	Signature	Date
Claire Wainwright	Principal Investigator	The University of Queensland		5th May 2026
Katherine Lee	Senior Biostatistician	Murdoch Children's Research Institute		5 May 2026

2. INTRODUCTION

2.1. STUDY SYNOPSIS

The *Mycobacterium abscessus* group (MABS) are a species of non-tuberculous mycobacteria (NTM) found in water and soil habitats that exhibit high levels of intrinsic multi-drug resistance. Individuals with underlying inflammatory lung diseases are more susceptible to *Mycobacterium abscessus* pulmonary disease (MABS-PD), but MABS also affects patients with no underlying conditions. MABS-PD can result in significant morbidity, increased healthcare utilization, accelerated lung function decline, impaired quality of life (QoL) (ref), more challenging lung transplantation (ref), and increased mortality (ref). Of particular concern is the increasing prevalence of pulmonary infections occurring worldwide in patients with bronchiectasis and cystic fibrosis (CF).

There is no clinical trial evidence currently to guide therapy for MABS-PD, a complex and increasing health problem. Treatment regimens for MABS are highly variable, not evidence-based and involve complex, expensive and often poorly tolerated drug combinations for prolonged periods. The FOR*Ma*T trial seeks to provide answers to key questions by healthcare providers and patients on the timing and nature of treatments for the growing number of people infected with MABS, as well as the potential to model the progression of this condition in both treated and untreated patients (via the observational cohort). Furthermore, the trial will provide a platform for improving health outcomes for MABS patients and build a solid foundation for future testing of new therapeutics in the treatment of MABS.

Appendix A of the FORMaT trial describes the intervention program within FORMaT. Appendix A1 outlines the first iteration of the intervention program which aims to compare intensive and consolidation therapy that are currently used in practice to detemine the most effective intensive and consolidation therapy and the most effective treatment regimen used currently. This document outlines the SAP for Appendix A1. Appendix A2 of the FORMaT trial outlines a separate module that compares the efficacy of the same consolidation regimens for participants recruited into the trial after the intensive phase and randomised at the consolidation stage. The data from Appendix A2 will be incorporated into the analysis of Appendix A1 to provide additional information about the comparison of consolidation regimens. At the time of writing this statistical analusis plan (SAP) there were only Appendicies A1 and A2 within Appendix A. As new Appendicies are added to Appendix A (i.e. when Appendix A3 etc are added) new SAPs or addendums to the current SAP will be developed describing the analysis of the new Appendicies.

2.2. OVERALL OBJECTIVES OF APPENDIX A1

In this section we present the overall objectives of Appendix A1 of the FORMaT trial.

2.2.1. PRIMARY OBJECTIVE

To determine the optimal treatment for MABS-PD. The primary outcome for Appendix A1 is MABS clearance from respiratory samples with tolerance at Final Outcome (undertaken at 56 weeks for participants who received short intensive therapy (and at 62 weeks for participants who received prolonged intensive therapy).

2.2.2. SECONDARY OBJECTIVES

1. To examine the probability of microbiological clearance at Final Outcome (irrespective of toxicity) for participants according to treatment path.

2. To describe the safety of the treatment combinations in patients with MABS.
3. To describe the change in Forced Expiratory Volume in one second (FEV1) z-score at Final Outcome compared with screening in patients by treatment path and for those who do and who do not clear MABS at Final Outcome.
4. To phenotype the structural abnormalities of chest Computed Tomography (CT)s of MABS patients and examine changes in chest CT scores (bronchiectasis, trapped air, % disease) between screening and Final Outcome by treatment path and between those who clear and those who do not clear MABS at Final Outcome.
5. To describe the predictive value of structural abnormalities on Screening CTs for sputum conversion and for progression of structural changes in relation to treatment path.
6. To describe change in 6 Minute Walk Distance (6MWD) for adult participants from screening to Final Outcome according to treatment path and in participants who do and do not clear MABS at Final Outcome.
7. To describe the change in Health-Related Quality of Life (HRQoL) for participants with CF (using the Cystic Fibrosis Questionnaire-Revised (CFQ-R)) at Final Outcome compared with screening according to treatment path and in those that do and those that do not clear MABS at Final Outcome.
8. To describe general HRQoL (Short Form-36 (SF-36) Adults, St George Respiratory Questionnaire (SGRQ) and Pediatric Quality of Life Inventory (Peds-QL™) Children) at Final Outcome compared with screening according to treatment path and in those who do and who do not clear MABS at Final Outcome.
9. To examine the cost effectiveness of the proposed treatment combinations across both intensive and consolidation phases of the trial.
10. To examine causes for early withdrawal from MABS-PD treatment due to reasons other than poor tolerance as defined in the primary objectives.

2.2.3. EXPLORATORY OBJECTIVES

- To examine MABS clearance status at 12 months after Final Outcome by treatment path.

2.3. NESTED STUDY OBJECTIVES

2.3.1. SHORT INTENSIVE THERAPY

Primary objective:
To compare the microbiological clearance of MABS from respiratory samples collected at 4 weeks with good tolerability assessed at the end of short intensive therapy:

A1.1.1: with the use of inhaled amikacin (IA) (Arm B) compared with the use of intravenous amikacin (IVA) (Arm A)

A1.1.2: without (Arm C) and with the addition of clofazimine (Arm A) to standard intravenous (IV) treatment

Secondary objectives: To compare the following outcomes between participants

A1.1.1: with the use of IA (Arm B) compared with the use of IVA (Arm A)

A1.1.2: without (Arm C) and with the addition of clofazimine (Arm A) to standard IV treatment

1. Microbiological clearance from respiratory samples collected at 4 weeks (irrespective of toxicity) assessed at the end of short intensive therapy.
2. Safety in the short intensive therapy phase (measured until the end of short intensive).
3. Change in FEV1 z-score at end of short intensive versus at Screening.

4. Change in HRQoL (CFQ-R) for participants with CF at end of short intensive versus at Screening.
5. Change in HRQoL (SF-36 (Adults), SGRQ and Peds-QL™ (Children)) for participants between Screening and end of short intensive therapy.
6. Cost effectiveness during short intensive therapy
7. Causes for early withdrawal from MABS-PD treatment due to reasons other than poor tolerance as defined in the primary objectives.

2.3.2. SHORT VS PROLONGED INTENSIVE

Primary objective:
To compare the microbiological clearance from respiratory samples collected at 10 weeks with good tolerability assessed at the end of prolonged intensive (for those randomised to prolonged intensive) or at 12 weeks (for those randomised to immediate consolidation) between patients randomised to short vs prolonged intensive therapy who have ongoing MABS positive cultures at week 4.

Secondary objectives:
To compare:

1. Microbiological clearance from samples collected at 10 weeks (irrespective of toxicity) in prolonged intensive therapy compared with short intensive + immediate consolidation therapy in patients who had MABS positive cultures from samples collected at 4 weeks.
2. Safety of prolonged intensive therapy compared with short intensive + immediate consolidation therapy.
3. Change in FEV1 z-score between screening and end of prolonged intensive therapy or 12 weeks in participants that received prolonged intensive compared with short intensive + immediate consolidation who had MABS positive cultures from samples collected at 4 weeks.
4. Change in FEV1 z-score between screening and end of prolonged intensive therapy or 12 weeks in participants still culture positive for MABS at 10 weeks compared with those who have cleared MABS at 10 weeks.
5. Change in CT scan BEST-NTM parameters, between screening and end of prolonged intensive therapy (for those allocated to prolonged intensive) or 12 weeks (for those allocated to immediate consolidation).
6. Change in 6MWD between screening and end of prolonged intensive therapy or 12 weeks in adult participants who receive prolonged intensive compared with short intensive and immediate consolidation therapy who had MABS positive cultures from samples collected at 4 weeks.
7. Change in HRQoL (CFQ-R) for participants with CF between screening and end of prolonged intensive therapy or 12 weeks in participants who received prolonged intensive compared with short intensive + immediate consolidation therapy who had MABS positive cultures from samples collected at 4 weeks.
8. Change in general HRQoL (SF-36 (Adults), SGRQ and Peds-QL (children)) between screening and end of prolonged intensive therapy or 12 weeks in prolonged intensive therapy compared with short intensive and immediate consolidation therapy in patients who had MABS positive cultures at 4 weeks.
9. Cost effectiveness over a 12-week period of prolonged intensive compared with short intensive and immediate consolidation for those who remain MABS positive based on samples collected at 4 weeks.

And

10. To examine causes for early withdrawal from MABS-PD treatment due to reasons other than poor tolerance as defined in the primary objectives in prolonged intensive compared with

short intensive and immediate consolidation in patients who had MABS positive cultures based on samples collected at 4 weeks.

2.3.3. CONSOLIDATION

Primary objective:
To compare the microbiological clearance with good tolerability of MABS between patients allocated to consolidation therapy with oral treatment (Consolidation Arm a) and consolidation therapy with oral treatment and additional IA (Consolidation Arm b) at Final Outcome. Final Outcome will vary and will be at Week 56 or 62 depending on whether the patient had prolonged intensive therapy and started consolidation at Week 6 or at Week 12 of the trial and will be at Week 50 for those in the Consolidation Only Study (Appendix A2).

Secondary objectives:
To compare:

1. Microbiological clearance (irrespective of toxicity) at Final Outcome between Consolidation Arm a and Consolidation Arm b
2. Safety between Consolidation Arm a and Consolidation Arm b.
3. Change in FEV1 z-score between R-Con (randomisation to consolidation arm) and Final Outcome between Consolidation Arm a and Consolidation Arm b.
4. Change in CT scan parameters (bronchiectasis, mucus plugging, airway wall thickening, atelectasis, % disease and air trapping), between R-Con (where available) and Final Outcome.
5. Change in 6MWD between Week 12 of the trial and Final Outcome between adult participants allocated to Consolidation Arm a and those allocated to Consolidation Arm b.
6. Change in HRQoL (CFQ-R) between R-Con and Final Outcome between Consolidation Arm a and Consolidation Arm b for participants with CF.
7. General HRQoL (SF-36 (Adults), SGRQ and Peds-QL™ (Children)) between R-Con and Final Outcome between Consolidation Arm a and Consolidation Arm b.
8. Cost effectiveness of consolidation phase between Consolidation Arm a and Consolidation Arm b.

And

9. To examine causes for early withdrawal from MABS-PD treatment due to reasons other than poor tolerance as defined in the primary objectives between Consolidation Arm a and Consolidation Arm b.

2.4. STUDY DESIGN

The intervention program within FORMaT is an iterative, multi-stage platform trial with innovative and adaptive properties to evaluate combinations of therapies for patients with MABS-PD. The trial has the capacity to add new treatments in the future and to eliminate therapies because of futility as they either lack efficacy or cause unacceptable toxicity.

Entry into the FORMaT trial can occur at two different levels:

1. participants of any age from their first MABS isolate and not receiving current MABS therapy are eligible to enroll in the observational cohort and;
2. participants of any age meeting the American Thoracic Society (ATS) criteria for the diagnosis of MABS-PD and are untreated for MABS-PD in the preceding 12 months are eligible to enroll in the intervention program (the trial).

The intervention program

Intervention program participants will be randomised to receive MABS-PD therapy combinations and will be followed up for a maximum of 62 weeks.

Appendix A1 describes the first iteration of the intervention program which compares the efficacy of current treatment regimens for MABS-PD. This appendix has three nested studies, each of which compares the efficacy of currently used treatments (see Figure 1). These nested studies are detailed in two modules considering the initial intensive therapy and the consolidation therapy:

Intensive Therapy Module

1. Appendix A1.1: Comparison of short Intensive Therapies:
   - Arm A (control)
     i. IV amikacin, and:
     ii. IV tigecycline, and;
     iii. IV imipenem or IV cefoxitin, and;
     iv. Oral azithromycin or oral clarithromycin, and;
     v. Oral clofazimine.
   - Arm B
     i. Inhaled amikacin, and:
     ii. IV tigecycline, and;
     iii. IV imipenem or IV cefoxitin, and;
     iv. Oral azithromycin or oral clarithromycin, and;
     v. Oral clofazimine.
   - Arm C
     i. IV amikacin, and:
     ii. IV tigecycline, and;
     iii. IV imipenem or IV cefoxitin, and;
     iv. Oral azithromycin or oral clarithromycin.

Note: For participants with confirmed mixed NTM infections (slow growers + MABS), ethambutol can be added to the treatment arms if required by the treating physician.

The specific comparisons of interest are

A1.1.1: Use of Inhaled Amikacin (IA, arm B) During Intensive Therapy to Replace Intravenous Amikacin (IVA, Arm A) in the Treatment of MABS-PD.

A1.1.2: The Use of Additional Clofazimine (Arm A) to Standard Intravenous Therapies (Arm C) during Intensive Therapy in the Treatment of MABS-PD.

2. Appendix A1.2: Compares prolonged intensive (12 weeks) versus immediate consolidation for patients with ongoing positive MABS cultures after completing 4 weeks of Intensive Therapy.

Consolidation Therapy Module

3. Appendix A1.3: Compares the use of oral therapy only or oral therapy and inhaled amikacin for Consolidation Therapy. Comparison of the two consolidation arms
   a. Consolidation Arm a (control):
      1. Oral clofazimine, and;
      2. Oral azithromycin or clarithromycin, and;
      3. In combination with one to three of the following oral antibiotics:
         a. Linezolid,
         b. Trimethoprim/sulfamethoxazole (co-trimoxazole),
         c. Bedaquiline,

d. Rifabutin,
e. Doxycycline,
f. Moxifloxacin.

b. Consolidation Arm b:
1. Inhaled Amikacin, and;
2. Oral clofazimine, and;
3. Oral azithromycin or clarithromycin, and;
4. In combination with one to three of the following oral antibiotics:
   a. Linezolid,
   b. Trimethoprim/sulfamethoxazole (co-trimoxazole),
   c. Bedaquiline,
   d. Rifabutin,
   e. Doxycycline,
   f. Moxifloxacin.

The Observational cohort

MABS infections may be transient, indolent or lead to clinical deterioration. An observational cohort will be established to enable biomarkers and clinical factors associated with clinical disease to be investigated. In addition, understanding background adverse events and health care utilisation in this untreated population provides additional population reference data for participants in the intervention program. Participants are eligible for the observational cohort if they have at least one positive MABS respiratory culture within 12 months and have not received treatment for MABS within 12 months except for use of macrolides for those with underlying CF or bronchiectasis. Patients in the observational cohort can enter the intervention program at any time if they meet all the eligibility criteria and none of the exclusion criteria for the intervention program.

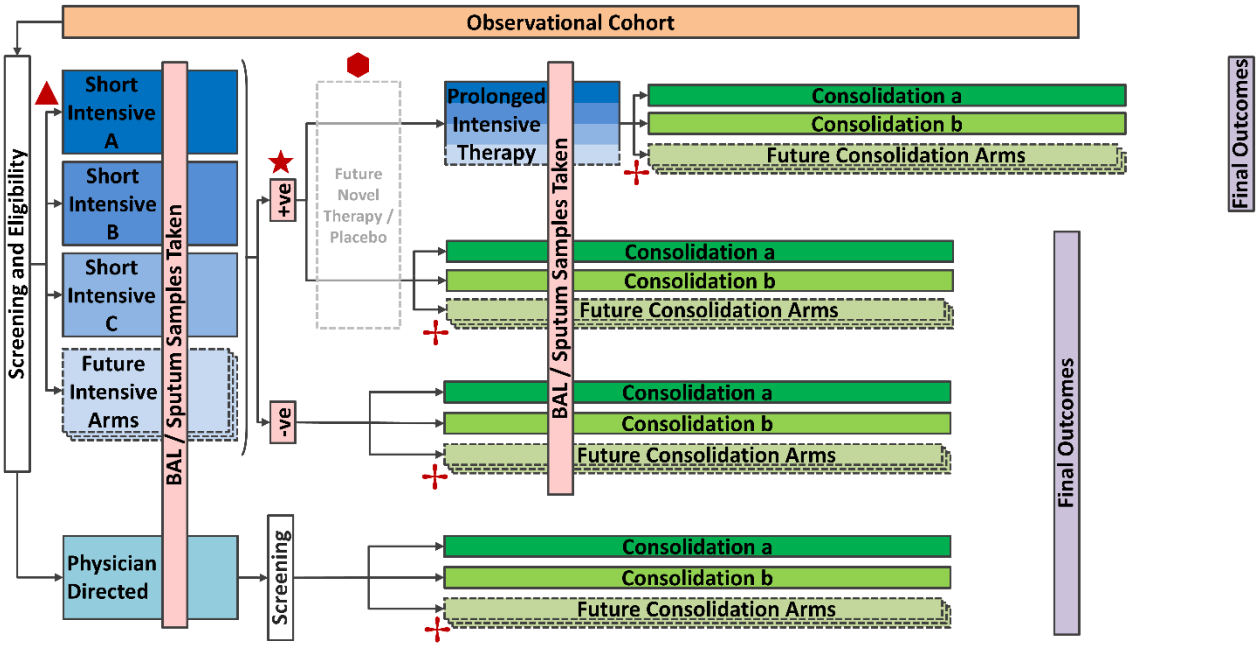


Figure 1: FOR*Ma*T participant flow diagram. Eligibility into the Intervention Program or Observational Cohort is determined at Screening. For the first iteration of the Intervention Program, there will be up to three randomisations between Screening and the Final Outcome Visit. Symbols (▲★⬢✢) indicate possible randomisation points (see the relevant appendix for further information on randomisation).

Assessing dynamic treatment regimens

When addressing the overall study objectives, we will use a Sequential Multiple Assignment Randomised Trial (SMART) analysis approach. Briefly, a SMART is a multi-stage trial design that can be used to construct effective dynamic treatment regimens (DTR) also known as adaptive interventions (AIs) or adaptive treatment strategies. With the initial three intensive arms and two consolidation arms, there are 24 embedded AIs in the initial design of FORMaT. These represent the different possibilities for initial intensive phase, what consolidation to use if negative after 6 weeks and what approach to use if positive after 6 weeks (where the format is (Type of intensive, "Type of consolidation if negative at 6 weeks", "Type of consolidation if positive at 6 weeks")):

AI #1: (Intensive IVA, "Consolidation: oral + IA", "Intensive IVA + Consolidation: oral + IA")
AI #2: (Intensive IVA, "Consolidation: oral + IA", "Intensive IVA + Consolidation: oral")
AI #3: (Intensive IVA, "Consolidation: oral + IA", "Consolidation: oral + IA")
AI #4: (Intensive IVA, "Consolidation: oral + IA", "Consolidation: oral")
AI #5: (Intensive IVA, "Consolidation: oral", "Intensive IVA + Consolidation: oral + IA")
AI #6: (Intensive IVA, "Consolidation: oral", "Intensive IVA + Consolidation: oral")
AI #7: (Intensive IVA, "Consolidation: oral", "Consolidation: oral + IA")
AI #8: (Intensive IVA, "Consolidation: oral", "Consolidation: oral")

AI #9: (Intensive IA, "Consolidation: oral + IA", "Intensive IA + Consolidation: oral + IA")
AI #10: (Intensive IA, "Consolidation: oral + IA", "Intensive IA + Consolidation: oral")
AI #11: (Intensive IA, "Consolidation: oral + IA", "Consolidation: oral + IA")
AI #12: (Intensive IA, "Consolidation: oral + IA", "Consolidation: oral")
AI #13: (Intensive IA, "Consolidation: oral", "Intensive IA + Consolidation: oral + IA")
AI #14: (Intensive IA, "Consolidation: oral", "Intensive IA + Consolidation: oral")
AI #15: (Intensive IA, "Consolidation: oral", "Consolidation: oral + IA")
AI #16: (Intensive IA, "Consolidation: oral", "Consolidation: oral")

AI #17: (Intensive C, "Consolidation: oral + IA", "Intensive C + Consolidation: oral + IA")
AI #18: (Intensive C, "Consolidation: oral + IA", "Intensive C + Consolidation: oral")
AI #19: (Intensive C, "Consolidation: oral + IA", "Consolidation: oral + IA")
AI #20: (Intensive C, "Consolidation: oral + IA", "Consolidation: oral")
AI #21: (Intensive C, "Consolidation: oral", "Intensive C + Consolidation: oral + IA")
AI #22: (Intensive C, "Consolidation: oral", "Intensive C + Consolidation: oral")
AI #23: (Intensive C, "Consolidation: oral", "Consolidation: oral + IA")
AI #24: (Intensive C, "Consolidation: oral", "Consolidation: oral")

For example, AI #1 represents the strategy of starting with Intensive IVA; using consolidation oral + IA if MABS is cleared at 6 weeks; continuing intensive IVA for six more weeks followed by oral + IA consolidation if not cleared at 6 weeks.

2.5. STUDY POPULATION

Details of the recruitment strategy and the inclusion/exclusion criteria can be found in the core protocol and Appendix A.

2.6. RANDOMISATION

There are three stages of randomisation in Appendix A1 of the intervention program:

1. Randomisation to Short Intensive (R-SI): At the start of the intensive phase, with all participants randomised between the 3 different intensive therapy arms for a period of 6 weeks.

2. Randomisation to Prolonged Intensive or Immediate Consolidation (R-PI/IC): ONLY for participants who are still MABS positive at the end of short intensive therapy (based on respiratory sampling collected at 4 weeks) and are able to continue with intensive therapy. Randomisation will occur at the end of week 6 and will allocate participants to either;
    1. Continue in the intensive therapy arm they are allocated to, for further 6 weeks which will be followed by consolidation, or;
    2. Immediately commence consolidation therapy.

3. Randomisation to Consolidation (R-Con): This randomisation will allocate participants to one of the two consolidation therapy arms either at
    1. week 6:
        - for patients who have cleared MABS at 6 weeks or;
        - for patients who remained MABS positive at 6 weeks and;
            - were randomised in randomisation 2 to start consolidation or;
            - were unable to continue with any IV treatment due to adverse events, or patient or physician acceptance
    2. week 12: for patients who were randomised to prolonged intensive therapy in randomisation 2.
    3. Day 1: for participants who are participating in Consolidation Only Therapy (Appendix A2)

Each randomisation will function as a 'quasi-separate' trial as well as being considered in combination (intensive + consolidation).

2.6.1. MINIMISATION

Randomisation at each stage will be conducted using the method of minimisation. The stratification factors being used in the minimisation procedure are:

1. Macrolide resistance*: Yes or no (weight = 50% in randomisations 1 and 2, 25% in randomisation 3).
2. Age: <12 years, 12-30 years and >30 years of age (weight = 20%).
3. Sex: Male or Female (weight = 7.5%).
4. Location: Asia Pacific as one stratum (includes Australia, New Zealand, Singapore and other Asian Pacific countries), United Kingdom and Republic of Ireland as one stratum, Europe as another stratum (includes Denmark, France, Netherlands), and Canada and the Americas as one stratum (weight = 7.5%). Parts of the world not listed above can be added into the regions based on closest proximity to the regions longitudinally.
5. Cystic Fibrosis Status: Yes or no (weight = 7.5%).
6. Mixed NTM infections at enrolment: Yes or no (weight = 7.5%).
7. MABS positive culture (randomization 3 only): Yes or no (weight = 25%)

See Section 6.3 of Master Protocol and Section 2.2 of Appendix F of the Master Protocol for more details.

2.6.2. BAYESIAN ADAPTIVE RANDOMISATION

For randomisation 1 (R-SI) where there are 3 interventions, Bayesian Adaptive Randomisation (BAR) will be used to update the allocation ratios between the intervention arms following pre-specified interim analyses. These updated allocation ratios will be governed by the posterior probability of each intervention being superior to the control invention. See Section 6 for more information.

2.7. SAMPLE SIZE ESTIMATION

The design (including the stopping rules) and the expected sample size of 300 participants within A1 was informed by Monte Carlo simulations. Details are provided in Appendix F (Section 3) of the Master Protocol.

3. OUTCOMES

3.1. PRIMARY OUTCOME

The primary outcome for Appendix A1 within the FORMaT intervention program is MABS clearance from respiratory sample(s) with tolerance at the Final Outcome. The same outcome will be assessed at three other time points during the trial representing the outcome of the various nested studies within the trial.

Tolerance is based on the Common Terminology Criteria for Adverse Events (CTCAE version 5.0). Only adverse events that are attributed as either "possibly", "probably", or "definitely" related to study drug will be assessed in the determination of tolerance. "Good" tolerance is defined as no adverse events occurring or only adverse events coded as CTCAE grades 1 and 2. "Poor" tolerance is defined as any adverse events attributed as possibly, probably, or definitely related to study drug coded as CTCAE grades 3, 4, or 5.

a. For comparisons of short intensive therapy at Week 6;
    a. MABS clearance:
        i. Three negative respiratory samples (sputum/induced sputum samples) collected at Week 4 OR
        ii. One negative bronchoalveolar lavage (BAL) or bronchial wash collected at Week 4.
    b. Tolerance: from the date of R-SI to end of short intensive defined as Date of Randomisation Prolonged Intensive or Immediate Consolidation (R-PI/IC) minus 1 day for those allocated prolonged intensive or Randomisation-Consolidation (R-Con) minus 1 day for those allocated to immediate consolidation.

b. For comparison of short and prolonged intensive therapy at Week 12 for those that are MABS positive at Week 4;
    a. Tolerance: From the date of R-SI to the date of R-Con minus 1 day (for those allocated to prolonged intensive) or Week 12 Visit date (for those allocated to immediate consolidation)
    b. MABS clearance:
        i. Three negative respiratory samples (sputum/induced sputum samples) collected at Week 10 OR
        ii. One negative BAL or bronchial wash collected at Week 10.

c. For comparisons of consolidation therapy;
    a. Tolerance:
        i. For participants in the short intensive group - from R-Con to Final Outcome (Week 56 Visit).
        ii. For participants in the prolonged intensive group- from R-Con to Final Outcome (Week 62 Visit).
        iii. For participants in Consolidation Only – from R-Con to Final Outcome (Week 50 Visit).

b. MABS clearance:
    i. Four consecutive negative samples (sputum/ induced sputum/ BAL or Bronchial wash) collected after the start of consolidation therapy with one of those specimens collected at least four weeks after completing consolidation therapy (i.e. the Final Outcome visit) OR
    ii. A negative BAL or bronchial wash collected at least four weeks after completion of consolidation therapy (i.e. the Final Outcome visit).

d. For the Final Outcome (for comparison of the overall regimens);
    a. Tolerance:
        i. For participants in the short intensive group - from the date of R-SI to Final Outcome (Week 56 Visit).
        ii. For participants in the prolonged intensive group- from the date of R-SI to Final Outcome (Week 62 Visit).
    b. MABS clearance:
        i. Four consecutive negative samples (sputum/ induced sputum/ BAL or Bronchial wash) collected after the start of consolidation therapy with one of those specimens collected at least four weeks after completing consolidation therapy (i.e. the final outcome visit) OR
        ii. A negative BAL or bronchial wash collected at least four weeks after completion of consolidation therapy (i.e. at the final outcome visit).

Note that "negative samples" imply MABS negative samples (i.e. the sample does not culture *M. abscessus*). Table 1 and Table 2 provide detailed description of how the MABS status will be determined from the culture samples for the above time points 1-2 and 3-4 respectively. The results of the samples collected at Week 4 and Week 10 visits will be available at Week 6 and Week 12 visits respectively. Visit windows of ±3 days will apply for the weeks 4, 6, 10 and 12 study visits. Visit windows of +14 days will apply for the Week 50, 56 and 62 study visits. Negative sputum/induced sputum samples need to be collected at least 1 week apart. For more details on study procedures including visit windows refer to FORMaT master protocol and relevant appendices.

For each of the above clearance definitions, a participant with a single positive sputum sample in any of the samples collected (in week 4 for short intensive, or week 10 for prolonged intensive) or a single positive sample in the last four sputum samples collected (in consolidation), will be classified as not reaching MABS clearance. If a BAL sample is collected at week 4 for short intensive or at week 10 for those subjects who remained positive for MABS at end of short intensive and were randomised either to prolonged intensive or immediate consolidation, or at the final outcome visit, this will be used to inform MABS clearance as BAL is a more reliable sampling method compared to sputum sampling. If the required number of respiratory samples is not collected and none of the samples collected are MABS-positive, and a BAL has not been undertaken, then the clearance outcome will be classified as missing.

Table 1: Summary of MABS status for different scenarios at end of short intensive and end of prolonged intensive phases.

	Any sample type	**Sputum sample**	**Induced sputum**	**Bronchial wash**	**BAL**
sample 1	+	-	-	-	-
sample 2	-	-	-	NA	NA
sample 3	-	-	-	NA	NA

MABS status	**MABS+**	**MABS-**	**MABS-**	**MABS-**	**MABS-**

'+' = culture M. abscesses=MABS positive; '-' = MABS negative; the trial monitoring team will aim to minimise missing samples. In the event of a missing sample (<3 sputum samples) a BAL/ Bronchial wash will be requested.

Table 2: Summary of MABS status for different scenarios at end of consolidation and at Final Outcome

Last 4 samples	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Sample 1	Any result	Any result	Any result	Any + sample in at least 1 of the 3 samples	Any - sample	< 3 negative samples and no + samples	Any result
Sample 2	Any result	Any result	Any result		Any - sample		Any result
Sample 3	Any result	Any result	Any result		Any - sample		Any result
Sample at final outcome visit (Week 56/62)	BAL-	BAL+	Sp+	Sp-	Sp-	Sp-	No sample
MABS status	**MABS-**	**MABS+**	**MABS+**	**MABS+**	**MABS-**	**Missing**	**Missing**

+ = culture M. abscesses=MABS positive; Sp=sputum samples, BAL=BAL samples, NK=Not Known/Cannot determine the outcome/Missing outcome; Sp represents both Sputum and Induced sputum samples. Bronchial wash samples are considered to be similar to BAL and hence given same rules; The trial monitoring team will aim to minimise missing samples. In the event of a missing sample (<3 sputum samples) a BAL/ Bronchial wash will be requested. ***Please note:*** *the MABS outcome at the End of Consolidation time point is the same as MABS outcome at the Final Outcome time point.*

3.2. SECONDARY OUTCOMES

a. MABS clearance at Final Outcome irrespective of toxicity

This will be the same as the primary outcome but will not include tolerability. As per the primary outcome, MABS clearance will be assessed at four time points during the trial representing the outcome of various nested studies within the trial. The four time points will be the same as defined in Section 2.1.

b. Safety of treatment combinations.

AEs and SAEs that are possibly, probably or definitely related to study medication. The definition of AEs and SAEs are given in Section 2.4 below.

Antimicrobial Resistance of MABS

The evolving antimicrobial resistance (AMR) profile of MABS isolates in response to study medication administration over the course of the study is a treatment emergent AE of interest. The AMR profile of MABS isolates cultured from respiratory samples collected from trial participants will be assessed longitudinally during the study to evaluate changes in susceptibility in response to the trial antimicrobial intervention (in the intervention group), and without antimicrobial intervention (in the Observational cohort).

Resistance patterns will be determined using standardised antimicrobial susceptibility testing (AST) methods performed on bacterial isolates obtained from participant clinical specimens at predefined timepoints (screening, end of short intensive, end of prolonged intensive, during consolidation and at final outcome).

Changes in resistance will be assessed by comparing: Minimum inhibitory concentrations (MICs) for relevant antimicrobial agents, and/or categorical susceptibility interpretations (susceptible, intermediate, resistant) according to internationally recognised breakpoints (e.g. CLSI or EUCAST).

The following variables are of interest:

- Emergence of new antimicrobial resistance, defined as a shift from susceptible/intermediate to resistant classification during or after treatment.
- Change in multidrug resistance status, defined by resistance to ≥2 antimicrobial classes.
- Acquisition of resistance-associated genetic markers, where applicable, identified by molecular methods (i.e. whole-genome sequencing).

Detailed analysis of AMR profile of MABS isolates and how this will be analysed will be outlined in a Genomics Analysis Plan. This will be made publicly available on GitHub.

c. Change in FEV1 z-score

Change in FEV1 z-score from the timepoints defined in the secondary objectives for each nested study will be calculated from the FEV1 from spirometry measurements (*spiro_fev*) taken at Screening, end of short intensive, end of prolonged intensive (for those randomized to prolonged intensive), Week 12 (for those randomised to immediate consolidation), start of consolidation therapy, and Final Outcome. These values will be converted to z-score using American Thoracic Society criteria and calculated from British reference values (http://www.lungfunction.org/growinglungs).

d. Change in CT-Scan

The CT-scans will be analysed using the Bronchiectasis Scoring Technique for Nontuberculous Mycobacteria (BEST-NTM) method. This score is a minor adaptation from the previously validated BEST-CT score for non-CF bronchiectasis, with the addition of cavitation in the NTM specific score [1]. The BEST-CT has been designed on the basis of the extensively validated Perth-Rotterdam Annotated Grid Morphometric Analysis (PRAGMA)-CF score [2], which is specific for CF disease. In the BEST-NTM scoring system the following sub-scores will be recorded in hierarchical order: (i) atelectasis and consolidation , (ii) bronchiectasis, (iii) mucus plugging and tree-in-bud , (iv) airway wall thickening , (v) cavity wall, (vi) cavity, (vii) ground glass opacities and (viii) emphysema and bullae al.. In all the sub-scores, the volume fraction is expressed as a percentage of total lung volume so that all sub-scores add to 100%. Percentage total disease score (% disease), which is a composite score reflecting all 8 components. There are therefore 9 CT measures in total: 8 sub-scores and the composite total disease score).

Changes in each of these measures from the timepoints defined in the secondary objectives will be calculated and are the variables of interest for CT.

e. Change in HRQoL

Change in HRQoL scores (total and sub-scores) at different time points as defined in the secondary objectives for each nested study will be calculated from below questionnaires:

- Patients with CF (CFQ-R respiratory domain)
- Adults (SF-36)
- Children (Peds-QL^{TM})

f. Cost effectiveness outcomes

These outcomes will be described in a separate SAP.

g. Change in 6-minute walk distance (6MWD)

The 6MWT measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. This outcome will be measured in adult participants (>=18 years of age) only. Change in 6MWD for adult participants at different time points defined in the secondary objectives for each nested study will be derived.

3.3. EXPLORATORY OUTCOMES

Participant's MABS clearance status 12 months after Final Outcome, where MABS clearance is defined as per the primary outcome.

3.4. DEFINITION OF SAFETY EVENTS

3.4.1. ADVERSE EVENTS (AES)

An AE is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. All adverse events (non-serious and serious) from the time of informed consent for the participation in the study until 30 days after the final study visit, will be captured in the study database.

The relationship, or attribution, of an AE to the trial therapies will be determined by the Investigator and coded according to the following definitions:

Unrelated: The adverse event is clearly not related to the investigational product.
Unlikely: The adverse event is doubtfully related to the investigational product.
Possibly: The adverse event may be related to the investigational product.
Probably: The adverse event is likely related to the investigational product.
Definitely: The adverse event is clearly related to the investigational product.

3.4.2. SERIOUS ADVERSE EVENTS (SAES)

SAEs will be defined as any untoward medical occurrence that at any dose:

i. Results in death.
ii. Is considered life threatening (i.e., in the view of the Investigator the adverse experience places the participant at immediate risk of death from the reaction, as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
iii. Requires hospital admission or prolongation of an existing hospitalisation.
iv. Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions).
v. Is a congenital anomaly/birth defect.
vi. Is an important medical event (i.e., when based upon appropriate medical judgment, the adverse experience may jeopardise the participant and may require medical or surgical intervention to prevent one of the above listed outcomes).

3.4.3. CODING OF AES

CTCAE version 5.0 will be applied in the trial safety database for coding of all AEs including SAEs. Coding for analysis will be completed by the FORMaT Pharmacovigilance Team. If an AE is unable to be coded and/or graded by the pharmacovigilance team or if coding/grading cannot be agreed upon, the independent Data Safety Monitoring Board (iDSMB) will be consulted to assess and code and/or grade the AE.

3.5. DATA MANAGEMENT

Data for Appendix A1 and A2 will be collected using various sources (medical records, questionnaires, CT scans etc.) will form the source documents. The site Investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of all trial data reported. Sites will enter the data required for the trial directly into an electronic case report form (eCRF) located in a study specific Research Electronic Data Capture (REDCap) FOR*Ma*T database. Data for the eCRF will be obtained directly from the medical record or source documents. It is crucial to the adaptive design of the trial that data is entered within 14 days of the study visit. Data cleaning will be performed weekly for the trial to ensure that the data are cleaned and ready for interim analyses. The REDCap FOR*Ma*T database will be hosted on Murdoch Children's Research Institute (MCRI) infrastructure.

3.6. ANALYSIS SOFTWARE

R statistical software (versions 4.0.3 or above), SAS 9.4 and Stata Release 18.0 or later will be used for the statistical analysis.

4. POPULATIONS FOR ANALYSIS

The population of interest in this analysis is the intention to treat (ITT) population.

The ITT population for the intervention program will comprise all participants who are randomised at one or more of the randomisation points within the trial and will be analysed according to the intervention arm that the participant was randomised to, regardless of the intervention they actually received. The ITT population will be used for all analyses of the intervention program.

When analysing data from the nested studies, the population of interest will be the ITT population within that nested study, which will consist of all participants randomised within that nested study who will be analysed according to the intervention arm that participant was randomised to, regardless of the intervention they actually received.

5. HANDLING OF MISSING DATA

All participants in the ITT population will be included in the analysis, with the exception of participants whose parents withdraw consent for the use of their child's data in the study where it is not ethical to include them.

As part of the descriptive analysis we plan to explore the missing data, in particular the amount of missing data in the outcome variables, the relationship between the baseline and 1) outcome variables and 2) missingness, and whether the missing data is different within the different treatment arms. This will enable us to consider the possible mechanism leading to the missing data which will be documented using a directed acyclic diagram. If there is a reasonable amount of missing data (>5%), the directed acyclic diagram will be used to guide the analysis which will use multiple imputation to handle the missing data in the primary analysis if indicated. Multiple imputation will be conducted using chained equations including treatment at each stage and baseline variables as auxiliary variables, and allowing for interactions between treatments and other variables in the imputation model where possible. Continuous variables will be imputed using linear regression, binary variables using logistic regression and ordinal variables using ordinal logistic regression. 50 imputed datasets will be generated and the results will be combined across imputed datasets using Rubin's rules. If multiple imputation is used to handle the missing data, the analysis will also be conducted using a complete

case analysis which will be presented as a sensitivity analysis. If there is <5% missing data and little evidence that the analysis would benefit from multiple imputation then the primary analysis will be a complete case analysis.

6. DESCRIPTIVE STATISTICS

6.1. RECRUITMENT AND FOLLOW-UP

The recruitment and follow-up of all the participants consented for the FORMaT study will be detailed in a CONSORT diagram. See Appendix B for an example. The patient disposition including early withdrawals, total movements from observational cohort to intervention program and the number completed the study will be summarised.

The recruitment of participants in each cohort will be presented by the study site and by randomisation stratum within each study arm in the nested studies (*Please see Section 5. Listings, Tables and Figures and Appendix B for an example*).

6.2. BASELINE CHARACTERISTICS

Baseline and demographic variables listed below will be summarised as a mean and standard deviation (SD) for continuous variables and number and proportions for categorical variables by the nested study arms (*See Section 5. Listings, Tables and Figures and Appendix B for an example*):

Sex; race and ethnicity; age category; child bearing potential; has the participant been diagnosed with CF; has the patient been diagnosed with CFTR related metabolic syndrome (CRMS) also known as CF screen positive, inconclusive diagnosis (CFSPID); site location; BMI z-score; Weight z-score; FEV1 z-score; CT bronchiectasis, CT mucus plugging, CT %disease, and CT trapped air.

6.3. PROTOCOL DEVIATIONS

Protocol deviations will be classified as minor or major. Minor protocol deviations do not carry significant ethical or administrative consequences. Major protocol deviations are those that affect participant's rights, safety or wellbeing and/or accuracy and reliability of the study data.

Examples of minor protocol deviations:

- Visit non-compliance (for example, study visit is conducted outside of the required timeframe or a procedure is missed) and there are no safety concerns;
- Incorrect execution of the consent form (for example, participant did not date their signature);
- Participant declines to complete scheduled research activities.

Examples of major protocol deviations:

- Use of unapproved recruitment procedures;
- Randomisation of an ineligible participant;
- Use of an unapproved version of the PICF;
- Visit non-compliance (e.g. study visit is conducted outside of the required timeframe or a participant monitoring visit is missed) and there are safety concerns;
- Loss of laptop computer that contained identifiable information about participants;
- Incorrect execution of obtaining consent (for example, consent was not obtained following ICH-GCP).

The number and percentage of participants with one or more protocol deviations and total number of deviations will be summarised within the intervention program overall, the nested studies and the observational cohort. Protocol deviations will also be summarised by the severity (minor and major) and type of deviation. The details of protocol deviations will be listed (*Please see Section 5. Listings, Tables and Figures and Appendix B for an example*).

6.4. ADHERENCE TO TREATMENT

Participant adherence to MABS-PD treatment in the intervention program will be measured via self-report using the 5-item Medication Adherence Rating Scale (MARS-5)[3, 4] at the timepoints outlined in the relevant appendices. The results from this questionnaire will be recorded in the Medication Adherence Questionnaire CRF. The total score across the 5 items will be summarised at each time point.

For certain jurisdictions, medication dispensing history data for participants will be requested from the relevant data custodians (e.g. in Queensland via the Public Health Authority application).
For these jurisdictions, participant adherence to the combination therapy will be assessed using the Medication Possession Ratio (MPR)[5-8]. Drug-specific MPRs will be calculated for each study medication using the formula:

$$\text{MPR} = \frac{\text{Total days' supply of medication dispensed}}{\text{Number of days in the trial treatment period}}$$

Where the total days' supply of medication dispensed for each medication will be calculated by dividing the total number of medication units dispensed to that participant (e.g. tablets, capsules, vials) by the number of medication units prescribed per day (in 24 hours) based on the study drug dosing (dose and frequency) entered into the Study Medication log in the EDC.

A regimen-level MPR will then be derived as the proportion of days during the study treatment period in which all prescribed study medications were available concurrently. Regimen-level MPR will be capped at 100%.

This will be calculated by treatment period as below:
Short Intensive treatment period:

- From the date of R-SI to end of short intensive defined as Date of Randomisation Prolonged Intensive or Immediate Consolidation (R-PI/IC) minus 1 day for those allocated prolonged intensive or Randomisation-Consolidation (R-Con) minus 1 day for those allocated to immediate consolidation.

Prolonged Intensive treatment period:

- From the date of R-SI to the date of R-Con minus 1 day (for those allocated to prolonged intensive) or Week 12 Visit date (for those allocated to immediate consolidation)

Consolidation treatment period:

- For participants in the short intensive group - from R-Con to Final Outcome (Week 56 Visit).
- For participants in the prolonged intensive group- from R-Con to Final Outcome (Week 62 Visit).
- For participants in Consolidation Only – from R-Con to Final Outcome (Week 50 Visit).

Entire treatment period:

- For participants in the short intensive group - from the date of R-SI to Final Outcome (Week 56 Visit).
- For participants in the prolonged intensive group- from the date of R-SI to Final Outcome (Week 62 Visit).

Treatment adherence will be reported descriptively only.

6.5. CONCOMITANT THERAPIES

All medications started and used during the trial will be recorded in detail in the study database and will be listed (*See Appendix of Listings, Tables and Figures*). WHODrug Global will be used to code all medication data to ensure correct and consistent terminology and coding of all medications in study participants. Concomitant medication data will be summarised for the different treatment arms.

7. INTERIM ANALYSIS FOR A1.1

7.1. PURPOSE OF INTERIM ANALYSES

FORMaT uses Bayesian Adaptive Randomisation (BAR) for the intensive phase of treatment (A1.1) which will change allocation ratios to increase allocation to intervention arms that are showing higher promise, fixing the proportion in the control arm at 1/3. At each interim analysis, the posterior probabilities of each intervention arm being superior to the control arm (Arm A) will be calculated; these posterior probabilities will then be used to recommend a change to the allocation ratio for ratification by the iDSMB. Intervention arms may be dropped from the trial if their posterior probability reaches one of the stopping rules (see section 6.3 for details). The interim analysis will be conducted by a statistician external to the trial team.

7.2. TIMING OF ANALYSES

Interim analyses will start once 60 participants have been randomised to intensive treatment and had six-week outcome recorded and then conducted after each 60 additional participants until the final sample size is reached.

7.3. STATISTICAL METHODS FOR INTERIM ANALYSIS

The interim analyses will use data collected during the trial, together with a non-informative Bayesian prior distribution, to make inference about the posterior probability that each intervention arm (B and C) is superior to the control arm (A) and create a recommended updated allocation ratio for each arm.

We define the following quantities that will be used for the interim analysis:

- p_A, p_B and p_C represent the probability of six-week clearance with tolerability for arms A, B and C;
- n_A, n_B, n_C represent the number of participants with six-week outcome observed at the interim on arms A, B, C;
- $n = n_A + n_B + n_C$ represents the current sample size at the interim analysis and N represents the total sample size planned for the arms currently in the intensive phase;
- Y_A, Y_B, Y_C represent the number of participants with six-week clearance with tolerability for arms A, B, C;

- $P(p_B > p_A|Y_A, Y_B, n_A, n_B)$ and $P(p_C > p_A|Y_A, Y_c, n_A, n_C)$ represent the posterior probabilities that arm B and arm C (respectively) has higher probability of six-week clearance with tolerability;
- π_A, π_B, π_C represent the updated allocation ratios produced by the BAR procedure.

The prior used for each six-week clearance with tolerability probability will be Beta(0.2,0.8). The posterior for p_i ($i \in \{A, B, C\}$) is $Beta(0.2 + Y_i, 0.8 + n_i - Y_i)$.

The posterior probability that arm i $\in \{B, C\}$ is superior to arm A for six-week clearance with tolerability, $P(p_i > p_A|Y_i, Y_A, n_i, n_A)$ will be calculated using the following formula:

$$P(p_i > p_A|Y_i, Y_A, n_i, n_A) = \int_0^1 f(x, 0.2 + Y_A, 0.8 + n_A - Y_A)\big(1 - F(x, 0.2 + Y_i, 0.8 + n_i - Y_i)\big)dx$$

Where f(x,a,b) and F(x,a,b) are respectively the probability density and cumulative density functions of a Beta(a,b) random variable evaluated at x. This can straightforwardly be found using the *integrate*, *dbeta*, and *pbeta* functions in R as follows:

```
differenceinbeta_givenx=function(x,alpha1,beta1,alpha2,beta2)
{
  return(dbeta(x,alpha1,beta1)*(1-pbeta(x,alpha2,beta2)))
}

#differenceinbeta integrates over the pdf to get the probability of second Beta function being higher than first
differenceinbeta=function(alpha1,beta1,alpha2,beta2)
{
 #integrates over sample space of first beta distribution and qbeta of the second distribution:

 int=integrate(differenceinbeta_givenx,lower=qbeta(1e-10,alpha1,beta1),upper=qbeta(1-1e-10,alpha1,beta1),alpha1=alpha1,beta1=beta1,alpha2=alpha2,beta2=beta2)$value

 return(int)
}
```

Once the two posterior probabilities $P(p_B > p_A|Y_B, Y_A, n_B, n_A)$ and $P(p_C > p_A|Y_C, Y_A, n_C, n_A)$ are found, the recommended allocations for future participants will be set as follows:

$$\pi_A = \frac{1}{3}$$

$$\pi_B = \frac{2}{3} \times \frac{P(p_B > p_A|Y_A, Y_B, n_A, n_B)^{\gamma\left(\frac{n}{N}\right)}}{P(p_B > p_A|Y_A, Y_B, n_A, n_B)^{\gamma\left(\frac{n}{N}\right)} + P(p_C > p_A|Y_A, Y_C, n_A, n_C)^{\gamma\left(\frac{n}{N}\right)}}$$

$$\pi_C = \frac{2}{3} \times \frac{P(p_C > p_A|Y_A, Y_C, n_A, Nn_C)^{\gamma\left(\frac{n}{N}\right)}}{P(p_B > p_A|Y_A, Y_B, n_A, n_B)^{\gamma\left(\frac{n}{N}\right)} + P(p_C > p_A|Y_A, Y_C, n_A, n_C)^{\gamma\left(\frac{n}{N}\right)}}$$

If the recommended allocation probability for an intervention arm falls below 5%, the iDSMB should recommend that this arm stops for futility.

7.4. INTERIM ANALYSIS REPORTING

Results from the interim analysis will be presented to the iDSMB in the following tables alongside other information that would be presented in an iDSMB report.

Table 6.1: Summary of six-week outcome for each intensive therapy arm

	Intensive A N=xx	**Intensive B N=xx**	**Intensive C N=xx**
Number MABS negative (n/%)	**x1 (X1%)**	**y1 (Y1%)**	**z1 (Z1%)**
Number with ≥ 1 SAE (n/%)	**x2 (X2%)**	**y2 (Y2%)**	**z2 (Z2%)**
Number meeting the primary outcome - clearance with tolerability (n/%)	**x3 (X3%)**	**y3 (Y3%)**	**z3 (Z3%)**

Table 6.2: Summary of BAR model posterior probability and recommended allocation ratio

	Intensive A	**Intensive B**	**Intensive C**
Posterior probability of superiority to arm A	**-**	**x1**	**y1**
Recommended allocation ratio	**1/3**	**x2**	**y2**

8. ANALYSIS OF THE OVERALL STUDY OBJECTIVES

8.1. PRIMARY OUTCOME

The final analysis will take place once the last follow-up visit is complete. Once all data queries have been resolved (as far as possible) the database will be locked and the final analysis will commence.

The aim of this analysis is to identify which AI gives the highest rate of MABS clearance with tolerability during the whole trial (analysed at the Final Outcome time point; 56 weeks for participants who received short intensive and at 62 weeks for participants who received prolonged intensive). However, given the high number of AIs, there are too many comparisons to make. There are 276 pairwise comparisons, which can be reduced to 192 if we decide to compare pairs of AIs starting with different interventions. This number can be further reduced to 128 pairwise comparisons if one of the initial treatments is treated as a standard/control intervention.

Given the high number of pairwise comparisons, we will instead estimate the rate of MABS clearance with tolerability for each of the 24 AIs. The AI with the highest rate will be identified as being the best intervention regimen.

All intercurrent events will be handled using the treatment policy strategy (with the exception of death which is an SAE and hence is part of the outcome definition which constitutes a composite strategy).

Generalised estimating equations (GEE)[9] will be used to fit a replicated-weighted logistic regression model on MABS clearance with tolerability at the end of the study[10]. The weights will be used since participants will be randomised with unequal allocation probabilities in different stages of the trial (due to the BAR). Furthermore, some observations will be replicated given that some participants will be compatible with more than AI. For instance, responders in the first four AIs (those receiving "Consolidation a") are compatible with four different AIs. Hence their data will contribute to multiple AIs. To account for both this replication and the unequal randomisation probabilities due to the use of BAR, inverse probability weights will be used. These weights reflect the inverse of the probability that a participant followed a given AI, conditional on their observed data and the trial's randomization scheme. The weights thus correct for differential assignment probabilities and ensure that each AI's estimated outcome is unbiased.

The following equation will be fitted using SAS software[11]:

$$logit(P(Y_i = 1|X)) = \beta_0 + \beta_1 Stage1Trt_i + \beta_2 Stage2TrtResp_i + \beta_3 Stage2TrtNoResp_i + \beta_4 Stage1Trt_i * Stage2TrtResp_i + \beta_5 Stage1Trt_i * Stage2TrtNoResp_i + \beta_6 Stage2TrtResp_i * Stage2TrtNoResp_i + \beta_7 Stage1Trt_i * Stage2TrtResp_i * Stage2TrtNoResp_i$$

Where, Y_i denotes the clearance status with tolerability for participant i at the end of the trial (1=clearance with tolerability,0=otherwise), $Stage1Trt_i$ = stage 1 treatment options, and $Stage2TrtResp_i$= stage 2 treatment options for responders, and $Stage2TrtNoResp_i$= stage 2 treatment options for non-responders.

This model will be fitted using GEE and an independent covariance matrix to obtain robust standard errors. The following SAS code will be used:

```
PROC GENMOD DATA=SMART DESC;
CLASS ID Stage1Trt Stage2TrtResp Stage2TrtNoResp;
MODEL Y= Stage1Trt Stage2TrtResp Stage2TrtNoResp Stage1Trt*Stage2TrtResp
Stage1Trt*Stage2TrtNoResp Stage2TrtResp*Stage2TrtNoResp
Stage1Trt*Stage2TrtResp*Stage2TrtNoResp/DIST=binomial LINK=logit;
SCWGT weight;
REPEATED SUBJECT=ID / TYPE=Independent;

RUN;
```

The "weight" statement in above codes allows to account for different allocation probabilities due to the BAR. Inverse probability weighting is used during computation. The repeated statement allows to obtain robust standard errors since some of the observations contribute to multiple AIs.

Only participants with complete information (complete cases) will be included in the above model.

From this model we will estimate MABS clearance with tolerability probability for each of the 24 AIs. This will be reported with a corresponding 95% confidence interval. The AI with the highest probability will be recommended. The following SAS code will be used to estimate different AIs (codes for the first AI):

```
ESTIMATE "AI1 (Intensive_IVA, Cons_oral+IA, Intensive_IVA+Cons_oral+IA)"
INT 1 Stage1Trt 0 0 1 Stage2TrtResp 0 1 Stage2TrtNoResp 0 0 0 0 0 0 0 1 Stage1Trt*Stage2TrtResp 0
0 0 0 0 1 Stage1Trt*Stage2TrtNoResp 0 0 0 0 0 0 0 0 0 0 0 1 Stage2TrtNoResp*Stage2TrtResp 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 1 Stage1Trt*Stage2TrtResp*Stage2TrtNoResp 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 1;
```

Results from SMART design analysis will be presented in the following tables:

Table 7.1: Adaptive interventions clearance with tolerability probabilities

Adaptive Intervention	**Estimated 56/62-week clearance with tolerability probability (95% CI)**
AI #1: (Intensive IVA, Consolidation: oral + IA , Intensive IVA + Consolidation: oral + IA")	x.xxx [x.xxx, y.yyy]
AI #2: (Intensive IVA, "Consolidation: oral + IA", "Intensive IVA + Consolidation: oral")	x.xxx [y.yyy, z.zzz]
AI #3: (Intensive IVA, "Consolidation: oral + IA", "Consolidation: oral + IA")	x.xxx [y.yyy, z.zzz]
⋮	⋮
AI #23: (Intensive IVA, "Consolidation: oral + IA", "Consolidation: oral")	x.xxx [y.yyy, z.zzz]
AI #24: (Intensive IVA, "Consolidation: oral", "Intensive IVA + Consolidation: oral + IA")	x.xxx [y.yyy, z.zzz]

8.2. SECONDARY OUTCOMES

All secondary outcomes will be presented separately in the 24 AIs and in patients with MABS+ or MABS- at Final Outcome, when appropriate, as means and standard deviations (SDs) for continuous outcomes and numbers and proportions for binary outcomes.

For the comparison between patients with MABS+ and MABS- at Final Outcome, ORs and mean differences will be estimated using logistic and linear regression respectively, adjusted for the minimisation factors as per the primary outcome unless stated otherwise. Results will be presented as an (adjusted) OR or mean difference, along with its 95% CI and p-value.

8.2.1. MICROBIOLOGICAL CLEARANCE AT FINAL OUTCOME, IRRESPECTIVE OF TOXICITY

The estimand of interest microbiological clearance at Final Outcome irrespective of toxicity (secondary objective 1) will be following the same analysis as mentioned in section 7.1.

Objective: To examine the microbiological clearance at Final Outcome (irrespective of toxicity) for participants according to treatment path.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population who are alive at Final Outcome
Treatment condition(s)	24 AIs
Variable (outcome)	MABS clearance during the whole trial (analysed at the Final Outcome time point; 56 weeks for participants who received short intensive and at 62 weeks for participants who received prolonged intensive) (defined in Section 2).
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE (except death): *Treatment policy strategy.*

	2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy.*
Summary measure	Estimated 56/62-week clearance probability within each AI (95% CI)

This outcome will be presented as estimated MABS clearance probability for each of the 24 AIs.

8.2.2. SAFETY OF THE TREATMENT COMBINATION

The estimand of interest for safety (secondary objective 2) is given in the table below.

Objective: To describe the safety of the treatment combinations in patients with MABS.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population
Treatment condition(s)	24 AIs
Variable (outcome)	AEs and SAEs that are possibly, probably or definitely related to study medication Change in MIC values for the study antimicrobials; emergence of new antimicrobial resistance, defined as a shift from susceptible/intermediate to resistant classification during or after treatment; Acquisition of resistance-associated genetic markers, where applicable, identified by molecular methods (i.e. whole-genome sequencing)
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *Composite strategy.*
Summary measure	The number and proportion of participants with AEs and SAEs that are possibly, probably or definitely related to study medication in each AI. Proportion of participants demonstrating a change in antimicrobial susceptibility of the target pathogen from baseline to end of treatment, as measured by MIC testing and standardised susceptibility categorisation.

Safety outcomes (AEs and SAEs related to study medications) will be presented as a number and the proportion of participants experiencing one or more events and the number of events in the 24 AIs.

8.2.3. CHANGE IN FEV1 Z-SCORE AT FINAL OUTCOME COMPARED WITH SCREENING (LUNG-FUNCTION)

The estimand of interest for the change in FEV1 z-score (secondary objective 3) is given in the table below.

Objective:

To describe the change in FEV1 z-score at Final Outcome compared with Screening in patients by treatment path and for those with MABS+ or MABS- at Final Outcome	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population who are alive at Final Outcome
Treatment condition(s)	24 AIs; Patients with MABS+ or MABS- at Final Outcome
Variable (outcome)	The change in FEV1 z-score at Final Outcome versus Screening.
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy.*
Summary measure	Mean change scores for each treatment path and 95% CI; Mean change scores for patients with MABS+ or MABS- at Final Outcome and 95% CI.

The mean change scores will be presented for patients by treatment path (24 AIs), as well as for patients with MABS+ or MABS- at Final Outcome along with its SD. These analyses will be presented descriptively only. The change scores will be estimated using the FEV1 z-score at Final Outcome minus the FEV1 z-score at Screening.

8.2.4. CHANGE IN CT SCAN AT FINAL OUTCOME VS SCREENING

The estimands of interest for change in chest CT scores (secondary objective 4) are described in the table below.

Objective: To phenotype the structural abnormalities of chest CTs of MABS patients and examine changes in chest CT scores by treatment path and between those who do and do not clear MABS at Final Outcome.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population who are alive at Final Outcome
Treatment condition(s)	24 AIs; Patients with MABS+ or MABS- at Final Outcome
Variable (outcome)	The change in the 8 CT scan sub-scores and their composite score of total disease (as mentioned in section 2.2 d) at end of Final Outcome versus Screening.
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy.*
Summary measure	Mean change scores for each treatment path and 95% CI; Mean difference in change scores between patients with MABS+ or MABS- at Final Outcome and 95% CI.

The mean change scores for each CT parameter will be presented for each treatment path along with its 95% CI.

The mean difference in change score between patients with MABS+ or MABS- at Final Outcome will be estimated using a linear regression model adjusted for the minimisation variables where possible and baseline CT score. The (adjusted) mean difference and 95% CIs together with p-values will be presented.

8.2.5. PREDICTIVE VALUE OF STRUCTURAL ABNORMALITIES ON SCREENING CTS

The estimands of interest for predictive value of structural abnormalities on Screening CTs for sputum conversion and for progression of structural changes in relation to therapy (secondary objective 5) are described in the table below.

Objective: To examine the predictive value of structural abnormalities on Screening CTs for sputum conversion and for progression of structural changes in relation to treatment path.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population who are alive at Final Outcome visit
Treatment condition(s)	24 AIs
Variable (outcome)	Sputum conversion (from positive to negative). The structural lung abnormalities in the CT scan at baseline ((i) atelectasis and consolidation, (ii) bronchiectasis, (iii) mucus plugging and tree-in-bud, (iv) airway wall thickening, (v) cavity wall, (vi) cavity, (vii) ground glass opacities, (viii) emphysema and bullae, (ix) their composite score total disease) will be used to predict the likelihood of sputum conversion during the study. Special focus will be given to the predictive value of the presence and size of cavitations on CT at start of study.
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy.*
Summary measure	ORs between structural abnormalities on Screening CT and the likelihood of sputum conversion from positive to negative during study period

ORs (for binary outcomes) or regression coefficients (for continuous outcomes) will be estimated to assess the association between structural abnormalities on screening CT and sputum conversion or changes in CT scores, using logistic and linear regression models, respectively. All models will be adjusted for the minimisation factors. Results will be presented as adjusted estimates, along with their 95% CIs and p-values.

8.2.6. CHANGE IN 6MWD

The estimand of interest for change in 6MWD (secondary objective 6) is given in the table below.

Objective:

To examine change in 6MWD for adult participants from Screening to Final Outcome according to treatment pathway and in participants who do and do not clear MSBS at Final Outcome.	
Estimand attribute	**Description**
Population	MABS positive adults (≥18 years of age) meeting trial eligibility criteria in the ITT population who are alive at Final Outcome
Treatment condition(s)	24 AIs; Patients with MABS+ or MABS- at Final Outcome
Variable (outcome)	The change in 6MWD from Screening to Final Outcome
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy.*
Summary measure	Mean change scores for each treatment path and 95% CI; Mean difference in change scores between patients with MABS+ or MABS- at Final Outcome and 95% CI.

The mean change scores will be presented for each treatment path separately along with its 95% CI.

The mean difference between patients with MABS+ or MABS- at Final Outcome will be estimated using a linear regression model adjusted for the minimisation variables where possible and baseline 6MWD. The (adjusted) mean difference and 95% CIs together with p-values will be presented for patients with MABS+ or MABS- at Final Outcome.

8.2.7. HEALTH RELATED QUALITY OF LIFE

The estimands of interest for HRQoL (secondary objectives 7 and 8) are given in the tables below.

Objective: To examine the change in HRQoL scores for participants with CF (using the Cystic Fibrosis Questionnaire-Revised (CFQ-R)) at Final Outcome compared with Screening according to treatment path and in those that do and those that do not clear MABS at Final Outcome.	
Estimand attribute	**Description**
Population	MABS positive participants with CF meeting trial eligibility criteria in the ITT population who are alive at Final Outcome
Treatment condition(s)	24 AIs; Patients with MABS+ or MABS- at Final Outcome
Variable (outcome)	The change in HRQoL scores at Final Outcome compared with Screening.
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason except death: *Treatment policy strategy.* 2. Death: *While alive strategy.* 3. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.*
Summary measure	Mean change scores for each treatment path and 95% CI; Mean difference in change scores between patients with MABS+ or MABS- at Final Outcome and 95% CI.

For this outcome, the ICE of death will be handled using a while on treatment strategy, as the primary interest is the HRQoL outcomes of participants who did not die as it does not make sense to assess

the QoL in participants who die whether related or unrelated to treatment. In this analysis, participants who die will be excluded from the analysis.

The mean change scores will be presented for each treatment path separately along with its 95% CI for participants with CF. The mean difference (MABS+ vs. MABS-) will be estimated using a linear regression model including a categorical variable for group (MABS+ compared to MABS-), adjusted for the minimisation variables where possible and baseline HRQoL. The (adjusted) mean difference and 95% CIs together with p-values will be presented for each comparison (MABS+ vs. MABS-) for participants with CF.

Objective: To examine general HRQoL scores at Final Outcome compared with Screening according to treatment path and in those that do and those that do not clear MABS at Final Outcome.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population who are alive at Final Outcome in 3 subgroups; 1. with CF (CFQ-R respiratory domain) 2. Adults (SF-36) 3. Children (Peds-QL™)
Treatment condition(s)	24 AIs; Patients with MABS+ or MABS- at Final Outcome
Variable (outcome)	The HRQoL scores at Final Outcome versus Screening, in the 3 domains described in the population attribute.
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason except death: *Treatment policy strategy.* 2. Death: *While alive strategy.* 3. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.*
Summary measure	Mean HRQoL scores and 95% CI in patients with MABS+ or MABS- at Final Outcome and within each subgroup; Mean difference in HRQoL scores between patients with MABS+ or MABS- at Final Outcome and 95% CI within each subgroup.

The mean HRQoL scores will be presented for each treatment path separately along with its 95% CI within each of the 3 subgroups. The mean difference (MABS+ vs. MABS-) will be estimated using a linear regression model including a categorical variable for group (MABS+ compared to MABS-), adjusted for the minimisation variables where possible and baseline HRQoL. The (adjusted) mean difference and 95% CIs together with p-values will be presented for each comparison (MABS+ vs. MABS-) within each subgroup.

8.2.8. COST EFFECTIVENESS

The cost effectiveness analysis will be described in a separate SAP.

8.2.9. CAUSE FOR EARLY WITHDRAWAL FROM MABS-PD TREATMENT

The causes for early withdrawal from MABS-PD treatment due to reasons other than poor tolerance as defined in the primary objectives will be described by listing the causes, such as social or logistic factors or new diagnosis complicating the clinical picture. This will be descriptive only.

8.2.10. SUBGROUP ANALYSES

Subgroup analyses will be performed on all secondary outcomes above. The pre-specified subgroups includes:

1. with CF and without CF.
2. Macrolide resistance (inducible or constitutive) and Macrolide sensitive (i.e. Macrolide resistance=No).

The results will be analysed as per the primary analysis of each outcome but with a main effect of the subgroup and an interaction between the subgroup and treatment. The treatment effect estimate, and its 95% CI, along with the p-value associated with the interaction term will be presented. It is noted that the trial is not powered to consider subgroups, thus these analyses will be considered exploratory.

8.3. EXPLORATORY OUTCOME

The estimand of interest microbiological clearance at 12 months after Final Outcome irrespective of toxicity is described in the table below.

Objective: To examine MABS clearance status at 12 months after Final Outcome (irrespective of toxicity) for participants according to treatment path.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population who are alive at Final Outcome
Treatment condition(s)	24 AIs
Variable (outcome)	MABS clearance status at 12 months after Final Outcome
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy.*
Summary measure	Estimated clearance probability (95% CI) within each AI.

This outcome will be presented as estimated MABS clearance probability for each of the 24 AIs. These results will be presented descriptively only.

9. ANALYSIS OF NESTED STUDIES

9.1. SHORT INTENSIVE THERAPY

9.1.1. PRIMARY OUTCOME

The estimand of interest for the primary outcome is given in the table below.

Objective: To compare the microbiological clearance without toxicity at end of short intensive I. with use of IA (Arm B) compared with use of IVA (Arm A) II. without the addition of clofazimine (Arm C) and with the addition of clofazimine (Arm A) to standard IV treatment.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population

Treatment condition(s)	6 weeks of intensive treatment (arms B or C compared to A)
Variable (outcome)	MABS clearance from respiratory samples collected at 4 weeks with good tolerability assessed at the end of short intensive therapy (defined in Section 2).
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *Composite strategy.*
Summary measure	ORs for treatment arm B/C vs A

The motivation for treating intercurrent events (ICEs) using a treatment policy strategy is because we wish to assess the efficacy of the 3 treatment arms if it were rolled out in practice.

The nested study's primary microbiological endpoint of clearance of MABS at 4 weeks with good tolerance assessed at the end of short intensive will be presented as the number and proportion in each intervention arm. The OR will be estimated using a logistic regression model of the primary outcome with a 3 level treatment variable, adjusted for the minimisation variables (Section 1.7). If there are convergence issues, minimisation variables that cannot be estimated or show high variance inflation factors will be removed from the analysis. The (adjusted) OR and 95% CI together with the p-value will be presented for each treatment comparison (B vs. A and C vs. A).

The Bayesian analysis that is used for the interim analyses (Section 6) will be repeated at the final analysis to provide the posterior probabilities that each intensive intervention arm is superior to control. In addition to this, the frequentist logistic regression described above will be implemented within a Bayesian framework using RJags. As recommended in Gelman et al[12], we will use Cauchy(0,10) as the prior for the intercept and independent Cauchy(0,2.5) priors for all other parameters. The posterior mean for the OR, 95% credible interval, and posterior probability OR>1 for each treatment comparison (B vs. A and C vs. A) will be presented.

The Bayesian analysis will be extended to provide predictive probabilities of a Phase III trial being successful, separately for arm B vs. A and C vs. A. To do this, 10000 posterior samples from the Bayesian model parameters will be taken. Each sample will then be used as the 'truth' for a simulated replicate which simulates outcomes from a 1:1 randomised trial with total sample size 600. Each replicate will be analysed using a frequentist logistic regression and success will be defined as a significant p-value at 0.05, two-sided. The proportion of replicates that have significant p-values will be used as the predictive probability of success.

SUPPLEMENTARY ANALYSIS

A supplementary analysis will be carried out where the strategy undertaken to handle treatment discontinuations due to tolerability (even if the AE causing the discontinuation is not recorded as grade 3+/SAE) is a composite strategy. Under this strategy, treatment intolerance will be combined with the primary outcome as a negative outcome.

SUBGROUP ANALYSES

Microbiological clearance with acceptable toxicity (the primary outcome) will be compared between the randomised groups (B vs. A and C vs. A) in pre-specified patient subgroups (secondary objective 1), namely:

1. Macrolide inducible resistance and Macrolide sensitive (i.e. Macrolide resistance=No).

2. Aged <12 years, 12-30 years and >30 years.
3. Male and female.
4. Located in Asia Pacific (1), United Kingdom and Republic of Ireland (2), Europe (3), Canada and the Americas (4).
5. with CF and without CF.
6. Mixed NTM infections at enrolment: yes or no
7. with and without constitutive macrolide resistance.

The number and proportion of participants who achieve MABS clearance with tolerance will be presented within each subgroup in each intervention arm. The analysis described in Section 8.1.1 for the primary outcome will be repeated for the above subgroups of participants by the inclusion of an interaction between each of the above variables and the intervention will be added to the analysis model one at a time. The treatment effect estimate, and its 95% CI, will be presented.

It is noted that the trial is not powered to consider subgroups, thus these analyses will be considered exploratory.

9.1.2. SECONDARY OUTCOMES

9.1.2.1. MICROBIOLOGICAL CLEARANCE AT 4 WEEKS, IRRESPECTIVE OF TOXICITY

The estimand of interest microbiological clearance at 4 weeks irrespective of toxicity (secondary objective 1) is given in the table below.

Objective: To compare the microbiological clearance at end of short intensive (irrespective of toxicity) I. with use of IA (Arm B) compared with use of IVA (Arm A) II. without the addition of clofazimine (Arm C) and with the addition of clofazimine (Arm A) to standard IV treatment.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population who are alive at 6 weeks
Treatment condition(s)	6 weeks of intensive treatment (arms B or C compared to A)
Variable (outcome)	MABS clearance from respiratory samples collected at 4 weeks (defined in Section 2).
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy.*
Summary measure	Adjusted OR for treatment arm B/C vs A with 95% CI.

This outcome will be presented as the number and proportion in each intervention arm. The OR for arm B vs. A and arm C vs. A will be estimated using a logistic regression model including a categorical variable for treatment, adjusted for the minimisation variables where possible (as for the primary

outcome). The (adjusted) OR and 95% CI together with the p-value will be presented for each treatment comparison (B vs. A and C vs. A).

9.1.2.2. SAFETY IN THE SHORT INTENSIVE THERAPY PHASE

The estimand of interest for safety (secondary objective 2) is given in the table below.

Objective: To examine the safety of short intensive therapy arms.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population
Treatment condition(s)	6 weeks of intensive treatment (arms B or C compared to A)
Variable (outcome)	AEs and SAEs that are possibly, probably or definitely related to study medication. Change in MIC values for the study antimicrobials; emergence of new antimicrobial resistance, defined as a shift from susceptible/intermediate to resistant classification during or after treatment; Acquisition of resistance-associated genetic markers, where applicable, identified by molecular methods (i.e. whole-genome sequencing)
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *Composite strategy*
Summary measure	The number and proportion of participants with AEs and SAEs that are possibly, probably or definitely related to study medication in each treatment arm. Proportion of participants demonstrating a change in antimicrobial susceptibility of the target pathogen from baseline to end of treatment, as measured by MIC testing and standardised susceptibility categorisation.

Safety outcomes (AEs and SAEs related to study medications) will be presented as a number and the proportion of participants experiencing one or more events and the number of events in the 3 treatment arms.

9.1.2.3. CHANGE IN FEV1 Z-SCORE AT WEEK 6 VERSUS DAY 1 (LUNG-FUNCTION)

The estimand of interest for the change in FEV1 z-score (secondary objective 3) is given in the table below.

Objective: To compare the change in FEV1 z-score at end of short intensive versus Screening I. with use of IA (Arm B) compared with use of IVA (Arm A) II. without the addition of clofazimine (Arm C) and with the addition of clofazimine (Arm A) to standard IV treatment.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population who are alive at 6 weeks

Treatment condition(s)	6 weeks of intensive treatment (arms B/C compared to A)
Variable (outcome)	The change in FEV1 z-score at end of intensive versus Screening.
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy*
Summary measure	Adjusted mean difference in change scores between treatment arms (B/C vs. A) and 95% CIs.

The mean change scores will be presented for each treatment arm separately along with its standard deviation (SD). The mean difference between arm B vs. A and arm C vs. A will be estimated using a linear regression model including a categorical variable for treatment, adjusted for the minimisation variables where possible (as per the primary outcome) and baseline FEV1 z-score. The (adjusted) mean difference and 95% CIs together with p-values will be presented for each treatment comparison (B vs. A and C vs. A).

9.1.2.4. HEALTH RELATED QUALITY OF LIFE

The estimands of interest for HRQoL (secondary objectives 4 and 5) are given in the table below.

Objective: To compare the change in HRQoL scores at the end of short intensive versus Screening; I. with use of IA (Arm B) compared with use of IVA (Arm A) II. without the addition of clofazimine (Arm C) and with the addition of clofazimine (Arm A) to standard IV treatment.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population who are alive at 6 weeks in 3 subgroups; 1. with CF (CFQ-R respiratory domain) 2. Adults (SF-36) 3. Children (Peds-QL™)
Treatment condition(s)	6 weeks of intensive treatment (arms B/C compared to A)
Variable (outcome)	The change in HRQoL scores at end of short intensive versus Screening, in the 3 domains described in the population attribute.
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason except death: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy.*
Summary measure	Adjusted mean difference in change scores between treatment arms (B/C vs. A) and 95% CI within each subgroup.

For this outcome, the ICE of death will be handled using a while on treatment strategy, as the primary interest is the HRQoL outcomes of participants who did not die as it does not make sense to assess

the QoL in participants who die whether related or unrelated to treatment. In this analysis, participants who die will be excluded from the analysis.

The mean change scores will be presented for each treatment arm separately along with its standard deviation (SD) within each of the subgroups. The mean difference (arm B vs. A and arm C vs. A) within each subgroup will be estimated using a linear regression model including a categorical variable for treatment (B, C compared with A), adjusted for the minimisation variables where possible (as per the primary outcome) and baseline HRQoL. The (adjusted) mean difference and 95% CIs together with p-values will be presented for each treatment comparison (B vs. A and C vs. A) within each subgroup.

9.1.2.5. COST EFFECTIVENESS

The cost effectiveness analysis will be described in a separate SAP.

9.1.2.6. CAUSES FOR EARLY WITHDRAWAL FROM MABS-PD TREATMENT

To examine causes for early withdrawal from MABS-PD treatment due to reasons other than poor tolerance as defined in the primary objectives a list of causes will be presented in each of the 3 treatment groups, including causes such as social or logistic factors or new diagnosis complicating the clinical picture. These data will be presented descriptively only.

9.1.2.7. SUBGROUP ANALYSES

Subgroup analyses will be performed on all secondary outcomes above for the following subgroups:

1. with CF and without CF.
2. Macrolide resistance (inducible or constitutive) and Macrolide sensitive (i.e. Macrolide resistance=No).

The data will be analysed as per the primary analysis of each outcome but the analysis model will include a main effect of the subgroup and an interaction between the subgroup and treatment. The treatment effect estimate within each subgroup will be presented with its 95% CI. It is noted that the trial is not powered to consider subgroups, thus these analyses will be considered exploratory.

9.2. DURATION OF INTENSIVE THERAPY FOR PATIENTS WITH ONGOING POSITIVE MABS CULTURES AFTER 4 WEEKS OF INTENSIVE THERAPY.

9.2.1. PRIMARY OUTCOME

The estimand of interest the primary outcome is given in the table below.

Objective: To compare the microbiological clearance from samples collected at 10 weeks with good tolerability between those who are allocated to prolonged intensive therapy and those allocated to immediate consolidation following short intensive therapy for participants who have ongoing MABS positive cultures at week 4.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population, who have completed short intensive therapy and remain MABS positive at week 4.
Treatment condition(s)	Prolonged intensive therapy (PI; 12 weeks of intensive therapy) compared to short intensive therapy (SI; 6 weeks of intensive therapy + 6 weeks of consolidation therapy)

Variable (outcome)	MABS clearance with good tolerability at end of prolonged intensive (for those randomised to prolonged intensive) or at 12 weeks (for those randomised to immediate consolidation) in patients who have ongoing MABS positive cultures at week 4 (defined in Section 2).
Strategies used to handle Intercurrent events	1. Treatment discontinuation due to AE grade 3+/SAE: *Composite strategy*. 2. Treatment discontinuation due to other reasons, including AEs below grade 3: *Treatment policy strategy*. 3. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy*. 4. Death: *Composite strategy*.
Summary measure	Adjusted ORs for treatment arm PI vs. SI with 95% CI.

The nested study's primary microbiological endpoint of clearance of MABS at 10 weeks with good tolerance measured at end of prolonged intensive (for those randomised to prolonged intensive) or at 12 weeks (for those randomised to immediate consolidation) will be presented as a number and proportion for participants allocated to prolonged intensive or short intensive. The OR will be estimated using logistic regression adjusted for the minimisation factors used in randomisation 2 (see section 1.7). If there are convergence issues, minimisation variables that cannot be estimated or show high variance inflation factors will be removed from the analysis. Results will be presented as an (adjusted) OR, along with its 95% CI and p-value.

SUPPLEMENTARY ANALYSIS

A supplementary analysis will be carried out where the strategy undertaken to handle treatment discontinuations due to tolerability (even if the AE causing the discontinuation is not recorded as grade 3+/SAE) will be a composite strategy. Under this strategy treatment intolerance will be combined with the primary outcome as a negative outcome.

SUBGROUP ANALYSES

Microbiological clearance with good tolerability (the primary outcome) will be compared between the Prolonged intensive therapy (PI; 12 weeks of intensive therapy) and the short intensive therapy (SI; 6 weeks of intensive therapy + 6 weeks of consolidation therapy) in pre-specified patient subgroups, namely participants:

1. Macrolide inducible resistance and Macrolide sensitive (i.e. Macrolide resistance=No).
2. Aged <12 years, 12-30 years and >30 years.
3. Male and female.
4. Located in Asia Pacific (1), United Kingdom and Republic of Ireland (2), Europe (3), Canada and the Americas (4).
5. with CF and without CF.
6. Mixed NTM infections at enrolment: yes or no
7. with and without constitutive macrolide resistance.

The number and proportion of participants who achieve MABS clearance with tolerance will be presented within each subgroup in each intervention arm. The analysis described in Section 8.2.1 for the primary outcome will be repeated for the above subgroups of participants by the inclusion of an interaction between each of the above variables and the intervention in the analysis model one at a time. The treatment effect estimate, and its 95% CI, within each subgroup will be presented.

It is noted that the trial is not powered to consider subgroups, thus these analyses will be considered exploratory.

9.2.2. SECONDARY OUTCOMES

All secondary outcomes will be presented separately in the two treatment groups, as means and standard deviations for continuous outcomes and numbers and proportions for binary outcomes. ORs and mean differences will be estimated using logistic and linear regression respectively, adjusted for the minimisation factors as per the primary outcome unless stated otherwise. Results will be presented as an (adjusted) OR or mean difference, along with its 95% CI and p-value.

9.2.2.1. MICROBIOLOGICAL CLEARANCE AT END OF PROLONGED INTENSIVE/12 WEEKS, IRRESPECTIVE OF TOXICITY

The estimand of interest for microbiological clearance at end of prolonged intensive/12 weeks (irrespective of toxicity, secondary outcome a) is described in the table below.

Objective: To compare the microbiological clearance at end of prolonged intensive (irrespective of toxicity) in prolonged intensive compared with short intensive + consolidation (for those randomised to immediate consolidation) in patients who had MABS positive cultures at 4 weeks.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population, who have completed short intensive therapy and remain MABS positive at week 4, and who are alive at week 12.
Treatment condition(s)	Prolonged intensive therapy (PI; 12 weeks of intensive therapy) compared to short intensive therapy (SI; 6 weeks of intensive therapy + 6 weeks of consolidation therapy)
Variable (outcome)	MABS clearance from respiratory samples at end of prolonged intensive (irrespective of toxicity) in prolonged intensive compared with short intensive + consolidation (for those randomised to immediate consolidation) in patients (defined in Section 2).
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy.*
Summary measure	Adjusted OR for treatment arm PI vs. SI with 95% CI.

9.2.2.2. SAFETY

The estimand of interest for safety (secondary outcome b) is described in the table below.

Objective:

To describe the safety in prolonged intensive compared with short intensive + consolidation in patients who had MABS positive cultures at 4 weeks.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population, who have completed short intensive therapy and remain MABS positive at week 4.
Treatment condition(s)	Prolonged intensive therapy (PI; 12 weeks of intensive therapy) compared to short intensive therapy (SI; 6 weeks of intensive therapy + 6 weeks of consolidation therapy)
Variable (outcome)	AEs and SAEs that are possibly, probably or definitely related to study medication Change in MIC values for the study antimicrobials; emergence of new antimicrobial resistance, defined as a shift from susceptible/intermediate to resistant classification during or after treatment; Acquisition of resistance-associated genetic markers, where applicable, identified by molecular methods (i.e. whole-genome sequencing)
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *Composite strategy.*
Summary measure	The number and proportion of participants with AEs and SAEs that are possibly, probably or definitely related to study medication in each treatment arm, and the number of events by treatment arm. Proportion of participants demonstrating a change in antimicrobial susceptibility of the target pathogen from baseline to end of treatment, as measured by MIC testing and standardised susceptibility categorisation.

9.2.2.3. CHANGE IN FEV1 Z-SCORE BETWEEN SCREENING AND END OF PROLONGED INTENSTIVE/12 WEEKS (LUNG-FUNCTION)

The estimand of interest for change in FEV1 z-score in patients randomised to the prolonged vs short intensive therapy with MABS positive cultures from samples collected at 4 weeks (secondary objective 3) is described in the table below.

Objective: To compare the change in FEV1 z-score from Screening to end of prolonged intensive (for those randomised to prolonged intensive) or Week 12 (for those randomised to immediate consolidation) in patients randomised to the prolonged vs short intensive therapy with MABS positive cultures from samples collected at 4 weeks.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population, who have completed short intensive therapy and remain MABS positive at week 4, and who are alive at week 12.
Treatment condition(s)	Prolonged intensive therapy (PI; 12 weeks of intensive therapy) compared to short intensive therapy (SI; 6 weeks of intensive therapy + 6 weeks of consolidation therapy)

Variable (outcome)	The change in FEV1 z-score between Screening and end of prolonged intensive (for those randomized to prolonged intensive) or Week 12 (for those randomised to immediate consolidation).
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy.*
Summary measure	Difference in mean change scores between treatment arms (PI vs. SI) and 95% CIs.

The mean change scores will be presented for each treatment arm separately along with its standard deviation (SD). The mean difference between PI vs. SI who had MABS positive cultures at 4 weeks, will be estimated using a linear regression model including a categorical variable for treatment, adjusted for the minimisation variables where possible (as per the primary outcome) and baseline FEV1 z-score. The (adjusted) mean difference and 95% CIs together with p-values will be presented for PI vs. SI.

The estimand of interest for change in FEV1 z-score between participants still culture positive for MABS at 10 weeks compared with those who have cleared MABS at 10 weeks (secondary objective 4) is described in the table below.

Objective: To compare the change in FEV1 z-score between Screening and end of prolonged intensive (for those randomised to prolonged intensive) or Week 12 (for those randomised to immediate consolidation) between those participants still culture positive for MABS at 10 weeks compared with those who have cleared MABS at 10 weeks.	
Estimand attribute	**Description**
Population	Participants meeting trial eligibility criteria in the ITT population, who have sample collected at 10 weeks, and who are alive at 10 weeks.
Treatment condition(s)	MABS positive vs. MABS cleared at 10 weeks
Variable (outcome)	The change in FEV1 z-score between Screening and end of prolonged intensive (for those randomized to prolonged intensive) or Week 12 (for those randomised to immediate consolidation).
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy.*
Summary measure	Difference in mean change scores between MABS positive vs. MABS cleared at 10 weeks and 95% CIs.

The mean difference between participants still culture positive for MABS at 10 weeks compared with those who have cleared MABS at 10 weeks, will be estimated using a linear regression model including a categorical variable for treatment, adjusted for the minimisation variables where possible (as per the primary outcome) and baseline FEV1 z-score. The (adjusted) mean difference and 95% CIs together with p-values will be presented.

9.2.2.4. CHANGE IN CT SCAN AT WEEK 12 VS SCREENING

The estimand of interest for change in CT scan parameters (secondary objective 5) is described in the table below.

Objective: To compare the change in BEST-NTM and LungQ CT scan parameters at end of prolonged intensive (for those randomized to prolonged intensive) or Week 12 (for those randomised to immediate consolidation) versus Screening between patients randomised to the prolonged vs short intensive who had MABS positive cultures at 4 weeks.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population, who have completed short intensive therapy and remain MABS positive at week 4 and survived at 12 weeks.
Treatment condition(s)	Prolonged intensive therapy (PI; 12 weeks of intensive therapy) compared to short intensive therapy (SI; 6 weeks of intensive therapy + 6 weeks of consolidation therapy).
Variable (outcome)	The change in BEST-NTM CT scan parameters ((i) atelectasis and consolidation, (ii) bronchiectasis, (iii) mucus plugging and tree-in-bud, (iv) airway wall thickening, (v) cavity wall, (vi) cavity, (vii) ground glass opacities, (viii) emphysema and bullae, (ix) their composite total disease score) and in LungQ CT parameters (B_{out}/A, B_{in}/A, B_{wt}/A, B_{wa}/B_{oa}, mucus plug count, VERA %-trapped air). at end of prolonged intensive (for those randomized to prolonged intensive) or Week 12 (for those randomised to immediate consolidation) versus Screening.
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy.*
Summary measure	Mean difference in change scores between treatment arms (PI vs. SI) and 95% CI.

The mean change in CT image analysis metrics will be presented for participants randomised to PI or SI along with its 95% CI.

The mean difference in change CT metrics between PI vs. SI who had MABS positive cultures at 4 weeks, will be estimated using a linear regression model adjusted for the minimisation variables where possible and baseline CT score. The (adjusted) mean difference and 95% CIs together with p-values will be presented.

9.2.2.5. CHANGE IN 6MWD

The estimand of interest for change in 6MWD (secondary objective 6) is described in the table below.

Objective: To compare the change in 6MWD at end of prolonged intensive (for those randomised to prolonged intensive) or Week 12 (for those randomised to immediate consolidation) versus Screening between patients randomised to the prolonged vs short intensive with MABS positive cultures at 4 weeks.	
Estimand attribute	**Description**

Population	MABS positive participants meeting trial eligibility criteria in the ITT population, who have completed short intensive therapy and remain MABS positive at week 4, and who are alive at 12 weeks.
Treatment condition(s)	Prolonged intensive therapy (PI; 12 weeks of intensive therapy) compared to short intensive therapy (SI; 6 weeks of intensive therapy + 6 weeks of consolidation therapy)
Variable (outcome)	The change in FEV1 z-score at end of prolonged intensive (for those randomized to prolonged intensive) or Week 12 (for those randomised to immediate consolidation) versus Screening.
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy.*
Summary measure	Difference in mean change scores between treatment arms (PI vs. SI) and 95% CI.

The mean change scores will be presented for each treatment arm separately along with its SD. The mean difference between PI vs. SI who had MABS positive cultures at 4 weeks, will be estimated using a linear regression model including a categorical variable for treatment, adjusted for the minimisation variables where possible (as per the primary outcome) and baseline 6MWD. The (adjusted) mean difference and 95% CIs together with p-values will be presented for PI vs. SI.

9.2.2.6. HEALTH RELATED QUALITY OF LIFE

The estimand of interest for change in HRQoL (secondary objectives 7 and 8) is described in the table below.

Objective: To compare the change in HRQoL scores at end of prolonged intensive (for those randomized to prolonged intensive) or Week 12 (for those randomised to immediate consolidation) versus Screening between patients randomised to the prolonged vs short intensive who had MABS positive cultures at 4 weeks.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population who have completed short intensive therapy and remain MABS positive at week 4, and are alive at 12 weeks in 3 subgroups; 1. with CF (CFQ-R respiratory domain) 2. Adults (SF-36) 3. Children (Peds-QL™)
Treatment condition(s)	Prolonged intensive therapy (PI; 12 weeks of intensive therapy) compared to short intensive therapy (SI; 6 weeks of intensive therapy + 6 weeks of consolidation therapy).
Variable (outcome)	The change in HRQoL scores at end of prolonged intensive (for those randomized to prolonged intensive) or Week 12 (for those randomised to immediate consolidation) versus Screening.
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason except death: *Treatment policy strategy.* 2. Death: *While alive strategy.*

	3. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.*
Summary measure	Mean difference in change scores between treatment arms (PI vs. SI) and 95% CI in each subgroup.

The mean change scores will be presented for each treatment arm separately along with SD within each of the subgroups. The mean difference (PI vs. SI) within each subgroup will be estimated using a linear regression model including a categorical variable for treatment, adjusted for the minimisation variables where possible (as per the primary outcome) and baseline HRQoL. The (adjusted) mean difference and 95% CIs together with p-values will be presented for treatment comparison (PI vs. SI) within each subgroup.

9.2.2.7. THE COST EFFECTIVENESS OF PROLONGED VS. SHORT INTENSIVE THERAPY.

The cost effectiveness analysis (secondary objective 9) will be described in a separate SAP.

9.2.2.8. CAUSES FOR EARLY WITHDRAWAL FROM MABS-PD TREATMENT

Causes for early withdrawal from MABS-PD treatment due to reasons other than poor tolerance as defined in the primary objectives will be described by presenting a list of causes, such as social or logistic factors or new diagnosis complicating the clinical picture, and the number of participants with each. These data will be presented descriptively only.

9.2.2.9. SUBGROUP ANALYSES

Subgroup analyses will be performed on all secondary outcomes above for the following subgroups:

1. with CF and without CF.
2. Macrolide resistance (inducible or constitutive) and Macrolide sensitive (i.e. Macrolide resistance=No).

The data will be analysed as per the primary analysis of each outcome but the analysis model will include a main effect of the subgroup and an interaction between the subgroup and treatment. The treatment effect estimate within each subgroup will be presented with its 95% CI. It is noted that the trial is not powered to consider subgroups, thus these analyses will be considered exploratory.

9.3. CONSOLIDATION THERAPY

When addressing the research question regarding consolidation therapy, the data from Appendix A1 will be combined with the data from Appendix A2. The summary statistics of demographic and baseline variables and the proportions of MABS positive and negative participants at the start of consolidation will be presented separately for the nested study A1 participants and Appendix A2 participants.

9.3.1. PRIMARY OUTCOME

The estimand of interest for the primary outcome is given in the table below.

Objective: To compare the microbiological clearance with good tolerability at Final Outcome visit, between consolidation therapy arms.	
Estimand attribute	**Description**

Population	MABS positive participants meeting trial eligibility criteria in the ITT population, who have either completed intensive therapy or who are unable to complete Intensive therapy due to a lack of tolerance, or who are starting consolidation therapy only study.
Treatment condition(s)	Consolidation arm a (Oral therapy only) compared to consolidation arm b (oral + inhaled therapy).
Variable (outcome)	MABS clearance with good tolerability at Final Outcome (defined in Section 2).
Strategies used to handle Intercurrent events	1. Treatment discontinuation due to AE grade 3+/SAE: Composite strategy. 2. Treatment discontinuation due to other reasons, including AEs below grade 3: Treatment policy strategy. 3. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): Treatment policy strategy. 4. Death: *Composite strategy*.
Summary measure	Adjusted ORs for treatment arm b vs a with 95% CI.

The nested study's primary microbiological endpoint of clearance of MABS with good tolerance at Final Outcome will be presented as a number and proportion separately for the consolidation therapy arms. The OR will be estimated using logistic regression adjusted for the minimisation factors as used in randomisation (see section 1.7), whether participants have undergone intensive therapy or directly started consolidation, and whether participants are MABS positive or MABS negative at the start of consolidation therapy. If there are convergence issues, minimisation variables that cannot be estimated or show high variance inflation factors will be removed from the analysis. Results will be presented as an (adjusted) OR, along with its 95% CI and p-value.

SENSITIVITY ANALYSIS

Since the data from Appendix A2 will also be analysed with data from A1, a sensitivity analysis will be carried out to determine whether the treatment effects for the participants in A1 only and participants in A2 (consolidation only) are similar by including an interaction between treatment group and whether the participant was in A1 or A2 (i.e. whether they participated in the intensive part of the study).

SUPPLEMENTARY ANALYSIS

A supplementary analysis will be carried out where the strategy undertaken to handle treatment discontinuations due to tolerability (even if the AE causing the discontinuation is not recorded as grade 3+/SAE) is a composite strategy. Under this strategy treatment intolerance will be combined with the primary outcome as a negative outcome.

SUBGROUP ANALYSES

Microbiological clearance with good tolerability (the primary outcome) will be compared between the consolidation therapy arms in pre-specified patient subgroups, namely participants:

1. Macrolide inducible resistance and Macrolide sensitive (i.e. Macrolide resistance=No).

2. Aged <12 years, 12-30 years and >30 years.
3. Male and female.
4. Located in Asia Pacific (1), United Kingdom and Republic of Ireland (2), Europe (3), Canada and the Americas (4).
5. with CF and without CF.
6. Mixed NTM infections at enrolment: yes or no
7. with and without constitutive macrolide resistance.

The number and proportion of participants who achieve MABS clearance with tolerance will be presented within each subgroup in each intervention arm. The analysis described in Section 8.3.1 for the primary outcome will be repeated for the above subgroups of participants by the inclusion of an interaction between each of the above variables and the intervention will be added to the analysis model one at a time. The treatment effect estimate, and its 95% CI, within each subgroup will be presented.

It is noted that the trial is not powered to consider subgroups, thus these analyses will be considered exploratory.

9.3.2. SECONDARY OUTCOMES

All secondary outcomes will be presented separately in the two treatment groups, as means and standard deviations for continuous outcomes and numbers and proportions for binary outcomes. ORs and mean differences will be estimated using logistic and linear regression respectively, adjusted for the stratification factors as per the primary outcome unless stated otherwise. Results will be presented as an (adjusted) OR or mean difference, along with its 95% CI and p-value.

9.3.2.1. MICROBIOLOGICAL CLEARANCE (IRRESPECTIVE OF TOXICITY)

The estimand of interest for microbiological clearance (irrespective of toxicity, secondary objective 1) is given in the table below.

Objective: To compare the microbiological clearance (irrespective of toxicity) at Final Outcome between consolidation therapy arms.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population, who have either completed intensive therapy or who are unable to complete Intensive therapy due to a lack of tolerance or who are starting consolidation therapy only study, and are alive at Final Outcome visit.
Treatment condition(s)	Consolidation arm a (Oral therapy only) compared to consolidation arm b (oral + inhaled therapy).
Variable (outcome)	MABS clearance from respiratory samples at Final Outcome.
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.*

	2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy.*
Summary measure	Adjusted ORs for treatment arms b vs a with 95% CI.

9.3.2.2. SAFETY

The estimand of interest for safety (secondary objective 2) is given in the table below.

Objective: To examine the safety of consolidation therapy arms.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population, who have either completed intensive therapy or who are unable to complete Intensive therapy due to a lack of tolerance or who are starting consolidation therapy only study.
Treatment condition(s)	Consolidation arm a (Oral therapy only) compared to consolidation arm b (oral + inhaled therapy).
Variable (outcome)	AEs and SAEs that are possibly, probably or definitely related to study medication
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *Composite strategy.*
Summary measure	The number and proportion of participants with AEs and SAEs that are possibly, probably or definitely related to study medication in each treatment arm, and the number of events per treatment arm.

9.3.2.3. CHANGE IN FEV1 Z-SCORE

The estimand of interest for change in FEV1 z-score (secondary objective 3) is given in the table below.

Objective: To compare the change in FEV1 z-score between R-Con (randomisation to consolidation) and Final Outcome between consolidation therapy arms.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population, who have either completed intensive therapy or who are unable to complete Intensive therapy due to a lack of tolerance or who are starting consolidation therapy only study and survived at Final Outcome visit.
Treatment condition(s)	Consolidation arm a (Oral therapy only) compared to consolidation arm b (oral + inhaled therapy).
Variable (outcome)	The change in FEV1 z-score at start of consolidation versus Final Outcome
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.*

	3. Death: *While alive strategy.*
Summary measure	Mean difference in change scores between treatment arms (b vs. a) and 95% CI.

Analyses will be as described above but also be adjusted for FEV1 z-score at start of consolidation and adjusted for MABS clearance at start of consolidation.

9.3.2.4. CHANGE IN CT SCAN

The estimands of interest for change in CT scan parameters (secondary objectives 4) are given in the table below.

Objective: To compare the change in CT scan parameters at Final Outcome versus week 12 OR Screening.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population, who have either completed intensive therapy or who are unable to complete intensive therapy due to a lack of tolerance and are alive at Final Outcome visit.
Treatment condition(s)	Consolidation arm a (Oral therapy only) compared to consolidation arm b (oral + inhaled therapy).
Variable (outcome)	The change in BEST-NTM CT scan parameters ((i) atelectasis and consolidation, (ii) bronchiectasis, (iii) mucus plugging and tree-in-bud, (iv) airway wall thickening, (v) cavity wall, (vi) cavity, (vii) ground glass opacities, (viii) emphysema and bullae, (ix) their composite total disease score) and in LungQ CT parameters (B_{out}/A, B_{in}/A, B_{wt}/A, B_{wa}/B_{oa}, mucus plug count, VERA %-trapped air at Final Outcome versus week 12.
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy.*
Summary measure	Difference in mean change scores between treatment arms (b vs. a) and 95% CI.

Analyses will be as described above but also be adjusted for the variable of interest at the start of consolidation.

9.3.2.5. CHANGE IN 6MWD

The estimand of interest for change in 6MWD (secondary objective 5) is given in the table below.

Objective: To compare the change in 6MWD between start of consolidation therapy and Final Outcome between consolidation therapy arms.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population, who have either completed intensive therapy or who are unable to complete Intensive therapy due to a lack of tolerance or who are starting consolidation therapy only study and survived at Final Outcome visit.
Treatment condition(s)	Consolidation arm a (Oral therapy only) compared to consolidation arm b (oral + inhaled therapy).

Variable (outcome)	The change in 6MWD at start of consolidation versus Final Outcome
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason including AE grade 3+/SAE: *Treatment policy strategy.* 2. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.* 3. Death: *While alive strategy.*
Summary measure	Mean difference in change scores between treatment arms (b vs. a) and 95% CI.

Analyses will be as described above but also be adjusted for 6MWD at start of consolidation and adjusted for MABS clearance at the start of consolidation.

9.3.2.6. HEALTH RELATED QUALITY OF LIFE (HRQOL)

The estimands of interest for change in HRQoL (secondary objectives 6 and 7) are given in the table below.

Objective: To compare the change in HRQoL scores at Final Outcome versus start of consolidation between consolidation therapy arms.	
Estimand attribute	**Description**
Population	MABS positive participants meeting trial eligibility criteria in the ITT population, who have either completed intensive therapy or who are unable to complete intensive therapy due to lack of tolerance and survived at Final Outcome visit; 1. with CF (CFQ-R respiratory domain) 2. Adults (SF-36), SGRQ 3. Children (Peds-QL™)
Treatment condition(s)	Consolidation arm a (Oral therapy only) compared to consolidation arm b (oral + inhaled therapy).
Variable (outcome)	The change in HRQoL scores at start of consolidation versus Final Outcome
Strategies used to handle Intercurrent events	1. Treatment discontinuation for any reason except death: *Treatment policy strategy.* 2. Death: *While alive strategy.* 3. Treatment non-compliance (intermittent or partial treatment adherence not resulting in discontinuation): *Treatment policy strategy.*
Summary measure	Mean difference in change scores between treatment arms (b vs. a) and 95% CI in the 3 subgroups.

Analyses will be as described above within the 3 subgroups but also be adjusted for HRQoL at the start of consolidation.

9.3.2.7. THE COST EFFECTIVENESS

The cost effectiveness analysis (secondary objective 8) will be handled in a separate SAP.

9.3.2.8. CAUSES FOR EARLY WITHDRAWAL FROM MABS-PD TREATMENT

Causes of early withdrawal from MABS-PD treatment due to reasons other than poor tolerance as defined in the primary objectives will be described using a list of causes and the number of each, such as social or logistic factors or new diagnosis complicating the clinical picture. These data will be presented descriptively only.

9.3.2.9. SUBGROUP ANALYSES

Subgroup analyses will be performed on all secondary outcomes above for the following subgroups:

1. with CF and without CF.
2. Macrolide resistance (inducible or constitutive) and Macrolide sensitive (i.e. Macrolide resistance=No).

The data will be analysed as per the primary analysis of each outcome but the analysis model will include a main effect of the subgroup and an interaction between the subgroup and treatment. The treatment effect estimate within each subgroup will be presented with its 95% CI. It is noted that the trial is not powered to consider subgroups, thus these analyses will be considered exploratory.

10. REFERENCES

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11. APPENDIX A: LISTINGS, TABLES AND FIGURES

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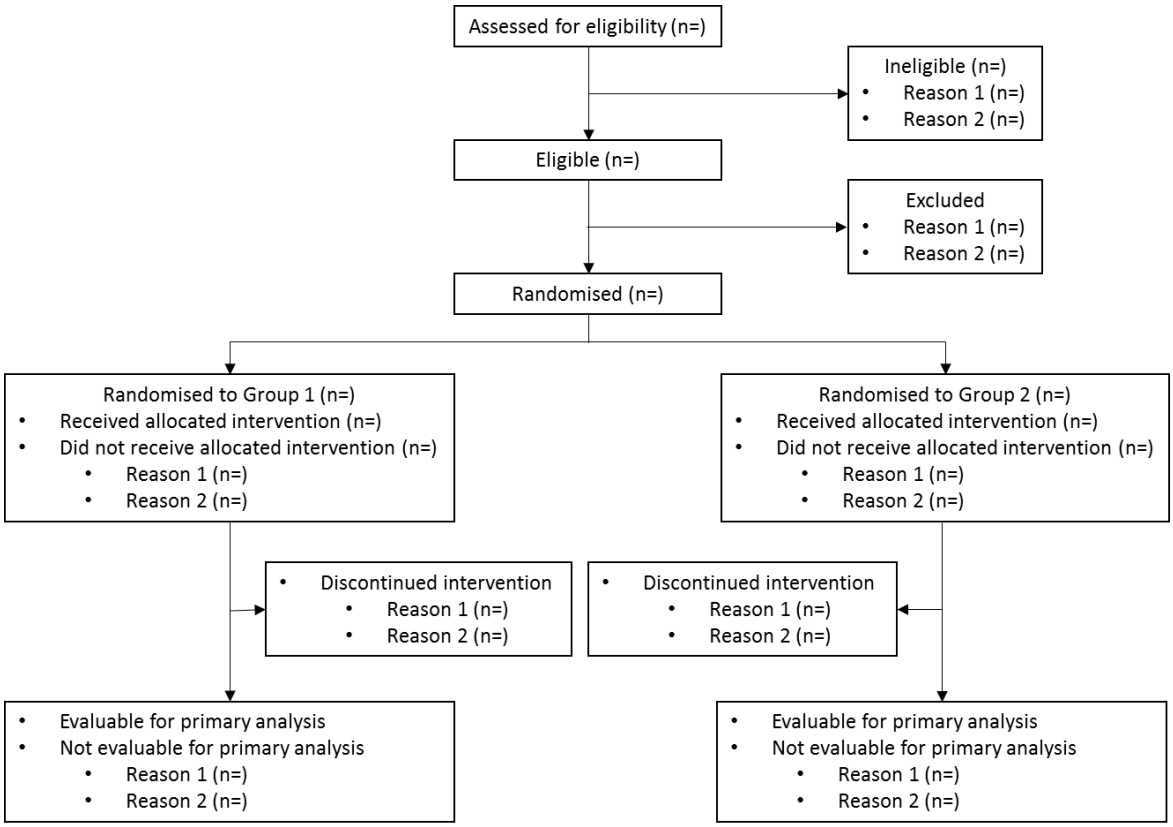
12. APPENDIX B: EXAMPLES, FIGURES AND TABLES

Example Figure: CONSORT flow diagram



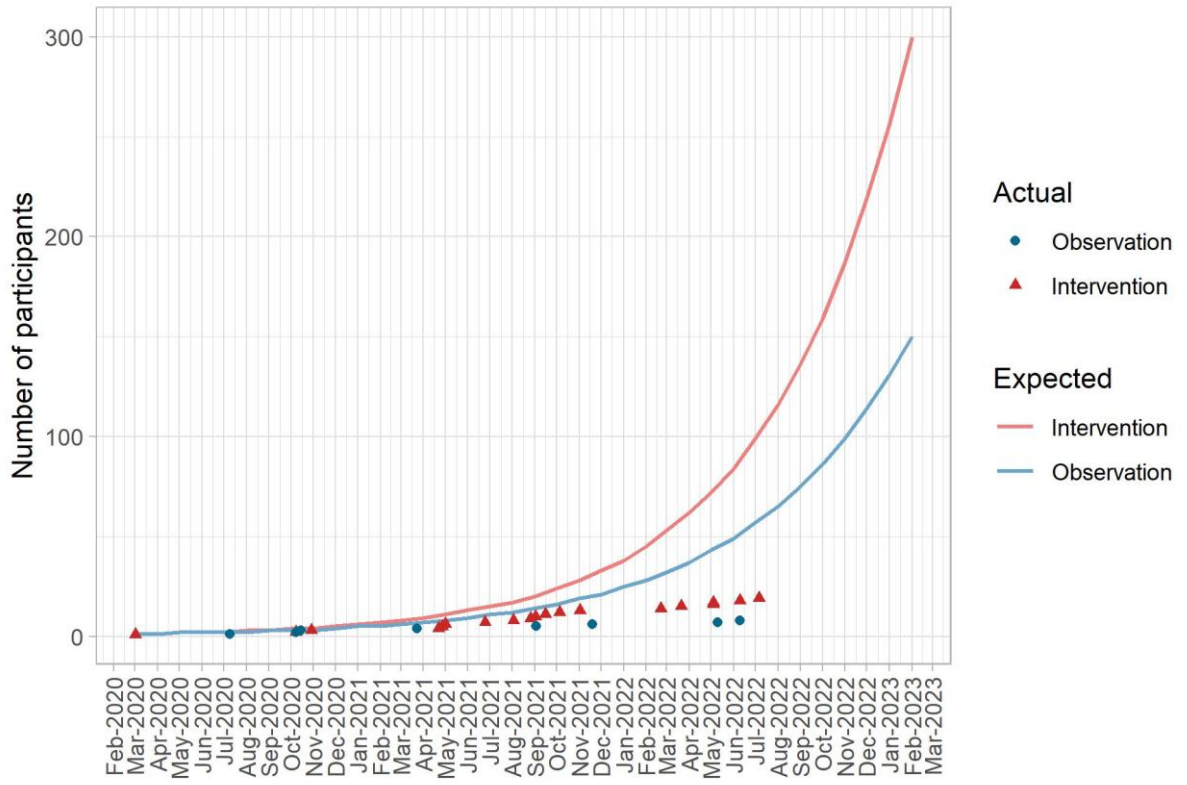


Figure 2: Number of participants recruited to date compared with projected recruitment (example only)

Table 1.0: FORMaT recruits as of xx xx xx

	Observational cohort	**Intervention program**	**Total**
Total recruited to date	**x**	**x**	**x**
Total observational to intervention	x	-	x
Total independent participants	-	-	x
Total withdrawn	x	x	x
Total completed	x	x	x
Current total in the study	**x**	**x**	**x**

Table 1.1: FORMaT recruiting sites as of xx xx xx

	Date first participant recruited	Observational cohort	Intervention program	Total
Total recruited to date	**-**	**x**	**x**	**x**
Queensland Children's Hospital	x	x	x	x
The Prince Charles Hospital	x	x	x	x
Gallipoli Medical Research Foundation	x	x	x	x
Princess Alexandra Hospital	x	x	x	x
Sunshine Coast University Hospital	x	x	x	x

Table 1.2: FORMaT recruits as of xx xx xx *at xx Hospital*

	Observational cohort	**Intervention program**	**Total**
Total recruited to date	**x**	**x**	**x**
Total observational to intervention	x	-	x
Total independent participants	-	-	x
Total withdrawn	x	x	x
Total completed	x	x	x
Current total in the study	**x**	**x**	**x**

Table 2.1: Recruitment by randomisation stratum by the intensive therapy arms (nested study A1.1)

	Intensive A N (%*)	**Intensive B N (%*)**	**Intensive C N (%*)**	**Total**
Number of patients randomised	**x (x%)**	**x (x%)**	**x (x%)**	**x**
Macrolide resistance				
Yes	x (x%)	x (x%)	x (x%)	x
No	x (x%)	x (x%)	x (x%)	x
Age				
<12 years	x (x%)	x (x%)	x (x%)	x
12-30 years	x (x%)	x (x%)	x (x%)	x
>30 years	x (x%)	x (x%)	x (x%)	x
Sex				
Male	x (x%)	x (x%)	x (x%)	x
Female	x (x%)	x (x%)	x (x%)	x
Location				
Asia Pacific	x (x%)	x (x%)	x (x%)	x
United Kingdom and Ireland	x (x%)	x (x%)	x (x%)	x
Europe	x (x%)	x (x%)	x (x%)	x
Canada and America	x (x%)	x (x%)	x (x%)	x
Cystic Fibrosis Status				
Yes	x (x%)	x (x%)	x (x%)	x
No	x (x%)	x (x%)	x (x%)	x
Mixed NTM infections at enrolment				
Yes	x (x%)	x (x%)	x (x%)	x
No	x (x%)	x (x%)	x (x%)	x

**Percentages of total participants within the stratum*

Table 3.1: Patients disposition by the intensive therapy arms (nested study A1.1)

	Intensive A N (%*)	**Intensive B N (%*)**	**Intensive C N (%*)**	**Total**
Consented	x (x%)	x (x%)	x (x%)	x
Number of infants randomised up to xx xx 20XX	x (x%)	x (x%)	x (x%)	x
Randomised in error	x (x%)	x (x%)	x (x%)	x
Withdrawn	x (x%)	x (x%)	x (x%)	x
Primary outcome available	x (x%)	x (x%)	x (x%)	x
Secondary outcome data available	x (x%)	x (x%)	x (x%)	x
Baseline data available	x (x%)	x (x%)	x (x%)	x

Table 4.1: Baseline characteristics by the intensive therapy arms (nested study A1.1)

		Intensive A N=xx	**Intensive B N=xx**	**Intensive C N=xx**	**Total N=xxx**
Number of patients with baseline data available		**xx**	**xx**	**xx**	**xxx**
BMI z-score	Mean (SD)[1]	xx (x)	xx (x)	xx (x)	xx (x)
Weight z-score	Mean (SD)[1]	xx (x)	xx (x)	xx (x)	xx (x)
FEV1 z score	Mean (SD)[1]	xx (x)	xx (x)	xx (x)	xx (x)
CT bronchiectasis	Mean (SD)[1]	xx (x)	xx (x)	xx (x)	xx (x)
CT % Disease	Mean (SD)[1]	xx (x)	xx (x)	xx (x)	xx (x)
CT Trapped Air	Mean (SD)[1]	xx (x)	xx (x)	xx (x)	xx (x)

[(1)]Mean and Standard Deviation (SD) are presented for the continuous variables.

Table 5.1: Protocol deviations during the first 6 weeks of intensive therapy (nested study A1.1)

	Severity of deviation												**Total**
	Uncategorised				**Minor**				**Major**				
	A N=x	**B N=x**	**C N=x**	**Total N=x**	**A N=x**	**B N=x**	**C N=x**	**Total N=x**	**A N=x**	**B N=x**	**C N=x**	**Total N=x**	**N=x**
Participants who had at least one protocol deviation	**x (xx%)**	**x (xx%)**	**x (xx%)**	**x (xx%)**	**x (xx%)**	**x (xx%)**	**x (xx%)**	**x (xx%)**	**x (xx%)**	**x (xx%)**	**x (xx%)**	**x (xx%)**	**x (xx%)**
Total number of protocol deviations	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Type of deviation													
Consent procedures	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Inclusion/Exclusion criteria	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Concomitant medication/Therapy	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Laboratory assessments/Procedures	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
- *Queensland Children's Hospital*	x	x	x	x	x	x	x	x	x	x	x	x	x
- *The Prince Charles Hospital*	x	x	x	x	x	x	x	x	x	x	x	x	x
- *Princess Alexandra Hospital*	x	x	x	x	x	x	x	x	x	x	x	x	x
- *Gallipoli Medical Research Foundation*	x	x	x	x	x	x	x	x	x	x	x	x	x
- *Sunshine Coast University Hospital*	x	x	x	x	x	x	x	x	x	x	x	x	x
Serious adverse event reporting	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Randomisation procedure	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Study drug dosing	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Visit schedule/Interval	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Other[3]	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)

[1]*Number (Percentage of total participants)*

[2]*Number (Percentages of total deviations)*

[3]*Details are provided in the appendix*

The below dummy table provides the summary of the Bayesian analyses of the primary endpoint.

Table 8.1: Summary of Bayesian analyses of six-week outcome

	Intensive B vs A	**Intensive C vs A**
Bayesian analysis		
OR (95% Credible Interval)	**x.xx (y.yy to z.zz)**	**x.xx (y.yy to z.zz)**
Posterior probability OR>1	**0.yy**	**0.yy**
Adjusted Bayesian analysis		
OR (95% Credible Interval)	**x.xx (y.yy to z.zz)**	**x.xx (y.yy to z.zz)**
Posterior probability OR>1	**0.yy**	**0.yy**
Bayesian predictive probability of phase III trial success	**0.yy**	**0.yy**

Table 6.1: Primary outcome data at 6 weeks by the intensive therapy arms (nested study A1.1)

		Intensive A N=xx	**Intensive B N=xx**	**Intensive C N=xx**	**Total N=xxx**
Primary outcome data available[(1)]		**xx**	**xx**	**xx**	**xxx**
Microbiological clearance of MABS-PD with tolerability	**(missing)**	**xx (xx%) (xx)**	**xx (xx%) (xx)**	**xx (xx%) (xx)**	**xx (xx%) (xx)**
Subgroups					
Macrolide resistance	Yes	xx (x%)	xx (x%)	xx (x%)	xx (x%)
	No	xx (x%)	xx (x%)	xx (x%)	xx (x%)
Cystic Fibrosis status	Yes	xx (x%)	xx (x%)	xx (x%)	xx (x%)
	No	xx (x%)	xx (x%)	xx (x%)	xx (x%)
Age	<12 years	xx (x%)	xx (x%)	xx (x%)	xx (x%)
	12-30 years	xx (x%)	xx (x%)	xx (x%)	xx (x%)
	>30 years	xx (x%)	xx (x%)	xx (x%)	xx (x%)

[(1)]Percentages are of those with data available

Table 7.1: Secondary outcome data by the intensive therapy arms (nested study A1.1)

	Intensive A N=xx	**Intensive B N=xx**	**Intensive C N=xx**	**Total N=xxx**
Secondary outcome data available[(1)]	**xx**	**xx**	**xx**	**xxx**
1. Microbiological clearance at final outcome (irrespective of toxicity)	**xx (x%)**	**xx (x%)**	**xx (x%)**	**xx (x%)**

Macrolide resistance	Yes	xx (x%)	xx (x%)	xx (x%)	xx (x%)
	No	xx (x%)	xx (x%)	xx (x%)	xx (x%)
Cystic Fibrosis status	Yes	xx (x%)	xx (x%)	xx (x%)	xx (x%)
	No	xx (x%)	xx (x%)	xx (x%)	xx (x%)
Age	<12 years	xx (x%)	xx (x%)	xx (x%)	xx (x%)
	12-30 years	xx (x%)	xx (x%)	xx (x%)	xx (x%)
	>30 years	xx (x%)	xx (x%)	xx (x%)	xx (x%)
2. Lung-function (FEV1 z-score compared with Day 0)		**xx (x)**	**xx (x)**	**xx (x)**	**xx (x)**
Macrolide resistance	Yes	xx (x)	xx (x)	xx (x)	xx (x)
	No	xx (x)	xx (x)	xx (x)	xx (x)
Cystic Fibrosis status	Yes	xx (x)	xx (x)	xx (x)	xx (x)
	No	xx (x)	xx (x)	xx (x)	xx (x)
Age	<12 years	xx (x)	xx (x)	xx (x)	xx (x)
	12-30 years	xx (x)	xx (x)	xx (x)	xx (x)
	>30 years	xx (x)	xx (x)	xx (x)	xx (x)
3. Chest CT scores - **CT %bronchiectasis**		**xx (x)**	**xx (x)**	**xx (x)**	**xx (x)**
Macrolide resistance	Yes	xx (x)	xx (x)	xx (x)	xx (x)
	No	xx (x)	xx (x)	xx (x)	xx (x)
Cystic Fibrosis status	Yes	xx (x)	xx (x)	xx (x)	xx (x)
	No	xx (x)	xx (x)	xx (x)	xx (x)
Age	<12 years	xx (x)	xx (x)	xx (x)	xx (x)
	12-30 years	xx (x)	xx (x)	xx (x)	xx (x)
	>30 years	xx (x)	xx (x)	xx (x)	xx (x)
Chest CT scores - **CT %trapped air**		**xx (x)**	**xx (x)**	**xx (x)**	**xx (x)**
Macrolide resistance	Yes	xx (x)	xx (x)	xx (x)	xx (x)
	No	xx (x)	xx (x)	xx (x)	xx (x)
Cystic Fibrosis status	Yes	xx (x)	xx (x)	xx (x)	xx (x)
	No	xx (x)	xx (x)	xx (x)	xx (x)
Age	<12 years	xx (x)	xx (x)	xx (x)	xx (x)
	12-30 years	xx (x)	xx (x)	xx (x)	xx (x)
	>30 years	xx (x)	xx (x)	xx (x)	xx (x)
Chest CT scores - **CT % disease**		**xx (x)**	**xx (x)**	**xx (x)**	**xx (x)**
Macrolide resistance	Yes	xx (x)	xx (x)	xx (x)	xx (x)
	No	xx (x)	xx (x)	xx (x)	xx (x)
Cystic Fibrosis status	Yes	xx (x)	xx (x)	xx (x)	xx (x)
	No	xx (x)	xx (x)	xx (x)	xx (x)
Age	<12 years	xx (x)	xx (x)	xx (x)	xx (x)
	12-30 years	xx (x)	xx (x)	xx (x)	xx (x)
	>30 years	xx (x)	xx (x)	xx (x)	xx (x)
4. The change in HRQoL compared with Day 0 - **CFQ-R (respiratory domain) for participants with CF**		**xx (x)**	**xx (x)**	**xx (x)**	**xx (x)**

Macrolide resistance	Yes	xx (x)	xx (x)	xx (x)	xx (x)
	No	xx (x)	xx (x)	xx (x)	xx (x)
Age	<11 years	xx (x)	xx (x)	xx (x)	xx (x)
	12-13 years	xx (x)	xx (x)	xx (x)	xx (x)
	Parent (child 6-11 years)	xx (x)	xx (x)	xx (x)	xx (x)
	>13 years	xx (x)	xx (x)	xx (x)	xx (x)
The change in HRQoL compared with Day 0					
- **SF-36**		**xx (x)**	**xx (x)**	**xx (x)**	**xx (x)**
Macrolide resistance	Yes	xx (x)	xx (x)	xx (x)	xx (x)
	No	xx (x)	xx (x)	xx (x)	xx (x)
Cystic Fibrosis status	Yes	xx (x)	xx (x)	xx (x)	xx (x)
	No	xx (x)	xx (x)	xx (x)	xx (x)
Age	<12 years	xx (x)	xx (x)	xx (x)	xx (x)
	12-30 years	xx (x)	xx (x)	xx (x)	xx (x)
	>30 years	xx (x)	xx (x)	xx (x)	xx (x)
The change in HRQoL compared with Day 0					
- **PedsQL**		**xx (x)**	**xx (x)**	**xx (x)**	**xx (x)**
Macrolide resistance	Yes	xx (x)	xx (x)	xx (x)	xx (x)
	No	xx (x)	xx (x)	xx (x)	xx (x)
Cystic Fibrosis status	Yes	xx (x)	xx (x)	xx (x)	xx (x)
	No	xx (x)	xx (x)	xx (x)	xx (x)
Age	5-7 years	xx (x)	xx (x)	xx (x)	xx (x)
	Parent (child 5-7 years)	xx (x)	xx (x)	xx (x)	xx (x)
	8-12 years	xx (x)	xx (x)	xx (x)	xx (x)
	Parent (child 8-12 years)	xx (x)	xx (x)	xx (x)	xx (x)
	>30 years	xx (x)	xx (x)	xx (x)	xx (x)

(1)Percentages are of those with data available. Mean (SD) are presented for the continuous variables.

Table 8.1: Adverse Events by the intensive therapy arms (nested study A1.1)

	Intensive A N=xx	**Intensive B N=xx**	**Intensive C N=xx**	**Total N=xxx**
Total number of adverse events (AE)	xx	xx	xx	xx(x%)
Patients who had at least one AE	xx	xx	xx	xx(x%)
Most common AEs ≥ 10% 0f patients in any randomised group N (%)	xx(xx%)	xx(xx%)	xx(xx%)	xx (x%)

Table 8.2: Serious Adverse Events during the first 6 weeks of the intensive therapy (nested study A1.1)

	Intensive A N=xx	**Intensive B N=xx**	**Intensive C N=xx**	**Total N=xxx**
Patients who had at least one SAE	x	x	x	xx (x%)
Most common SAEs ≥ 10% 0f patients in any randomised group N (%)	x (%)	x (%)	x (%)	xx (x%)
Total number of severe adverse events (SAE)	x	x	x	xx (x%)
Relationship to FORMaT intervention				
Not related	x (x%)	x (x%)	x (x%)	xx (x%)
Unlikely	x (x%)	x (x%)	x (x%)	xx (x%)
Possibly	x (x%)	x (x%)	x (x%)	xx (x%)
Definitely	x (x%)	x (x%)	x (x%)	xx (x%)
Outcome				
Death	x (x%)	x (x%)	x (x%)	xx (x%)
Trial drug withdrawal	x (x%)	x (x%)	x (x%)	xx (x%)
Trial drug interruption	x (x%)	x (x%)	x (x%)	xx (x%)
Type of SAE[2]				
Ototoxicity	x (x%)	x (x%)	x (x%)	x (x%)
QTc prolongation	x (x%)	x (x%)	x (x%)	x (x%)
Liver dysfunction	x (x%)	x (x%)	x (x%)	x (x%)
None of the above	x (x%)	x (x%)	x (x%)	x (x%)

[1]*Number (Percentage of total participants)*

[2]*Number (Percentages of total SAEs)*

Table 8.3: Ototoxicity adverse Events and serious adverse events by the intensive therapy arms (nested study A1.1)

	Intensive A N=xx	**Intensive B N=xx**	**Intensive C N=xx**	**Total N=xxx**
Total number of patients with hearing loss events	x	x	x	xx (x%)
Total number of patients with vestibular dysfunction events	x	x	x	xx (x%)
Relationship to FORMaT intervention				
Not related	x	x	x	xx (x%)
Unlikely	x	x	x	xx (x%)
Possibly	x	x	x	xx (x%)
Definitely	x	x	x	xx (x%)
Outcome				
Trial drug withdrawal	x	x	x	xx (x%)
Trial drug interruption	x	x	x	xx (x%)

Table 8.4: QTc prolongation adverse events and serious adverse events by the intensive therapy arms (nested study A1.1)

	Intensive A N=xx	**Intensive B N=xx**	**Intensive C N=xx**	**Total N=xxx**
Total number of children aged 0-17 years with QTc prolongation	x	x	x	xx (x%)
Total number adults aged ≥18 years with QTc prolongation	x	x	x	xx (x%)
Relationship to FORMaT intervention				
Not related	x	x	x	xx (x%)
Unlikely	x	x	x	xx (x%)
Possibly	x	x	x	xx (x%)
Definitely	x	x	x	xx (x%)
Outcome				
Severe Arrhythmia	x	x	x	xx (x%)
Trial drug withdrawal	x	x	x	xx (x%)
Trial drug interruption	x	x	x	xx (x%)
Death	x	x	x	xx (x%)

Table 8.5: Summary liver dysfunction adverse events and serious adverse events by the intensive therapy arms (nested study A1.1)

	Intensive A N=xx	**Intensive B N=xx**	**Intensive C N=xx**	**Total N=xxx**
Aspartate Aminotransferase increased AST (U/L)				
Grade 1: >ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	xx	xx	xx	xx (x%)
Grade 2: >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	xx	xx	xx	xx (x%)
Grade 3: >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	xx	xx	xx	xx (x%)
Grade 4: >20.0 x ULN if baseline was normal;	xx	xx	xx	xx (x%)

>20.0 x baseline if baseline was abnormal				
Alanine aminotransferase increased ALT (U/L)				
Grade 1: >ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	xx	xx	xx	xx (x%)
Grade 2: >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	xx	xx	xx	xx (x%)
Grade 3: >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	xx	xx	xx	xx (x%)
Grade 4: >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	xx	xx	xx	xx (x%)
Blood bilirubin Increased (umol/L)	xx	xx	xx	xx (x%)
Grade 1: >ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	xx	xx	xx	xx (x%)
Grade 2: >1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	xx	xx	xx	xx (x%)
Grade 3: >3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	xx	xx	xx	xx (x%)
Grade 4: >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	xx	xx	xx	xx (x%)
ALT or AST and Total Bilirubin				
ALT or AST >3ULN	xx	xx	xx	xx (x%)
Total bilirubin >2ULN	xx	xx	xx	xx (x%)

Outcome				
Trial drug withdrawal	x	x	x	xx (x%)
Trial drug interruption	x	x	x	xx (x%)

Table 8.6: Haematological adverse events and serious adverse events by the duration of intensive therapy (nested study A1.1)

	Intensive A N=xx	**Intensive B N=xx**	**Intensive C N=xx**	**Total N=xxx**
Anemia				
Grade 1: Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	x	x	x	xx (x%)
Grade 2: Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L				
Grade 3: Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated				
Grade 4: Life-threatening consequences; urgent intervention indicated	x	x	x	xx (x%)
Grade 5: Death				
White blood cell decreased				
Grade 1: <LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	x	x	x	xx (x%)
Grade 2: <3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L				
Grade 3: <2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L				
Grade 4: <1000/mm3; <1.0 x 10e9 /L	x	x	x	xx (x%)
Lymphocyte count decreased				
Grade 1: <LLN - 800/mm3; <LLN - 0.8 x 10e9/L	x	x	x	xx (x%)
Grade 2: <800 - 500/mm3; <0.8 - 0.5 x 10e9 /L				
Grade 3: <500 - 200/mm3; <0.5 - 0.2 x 10e9 /L				
Grade 4: <200/mm3; <0.2 x 10e9 /L	x	x	x	xx (x%)
Neutrophil count decreased				
Grade 1: <LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	x	x	x	xx (x%)
Grade 2: <1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L				
Grade 3: <1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L				
Grade 4: <500/mm3; <0.5 x 10e9 /L	x	x	x	xx (x%)
Platelet count				

Grade 1: <LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	x	x	x	xx (x%)
Grade 2: <75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L				
Grade 3: <50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L				
Grade 4: <25,000/mm3; <25.0 x 10e9 /L	x	x	x	xx (x%)
Relationship to FORMaT intervention				
Not related	x	x	x	xx (x%)
Unlikely	x	x	x	xx (x%)
Possibly	x	x	x	xx (x%)
Definitely	x	x	x	xx (x%)
Outcome				
Trial drug withdrawal	x	x	x	xx (x%)
Trial drug interruption	x	x	x	xx (x%)
Death	x	x	x	xx (x%)

Table x: Listing of protocol deviations

	Participant ID	Date of deviation	Type of deviation	Severity of deviation	Description of deviation	Protocol deviation result in participant withdrawal from the trial
1	xx	xx	xx	xx	xx	xx
2	xx	xx	xx	xx	xx	xx
3	xx	xx	xx	xx	xx	xx

Table 5.7: Line listing of all SAEs

	Participant ID	SAE ID	New SAE?	Reaction date	Most recent report date	Country	Sex	Age	Diagnosis of SAE	Outcome of SAE	Suspected aetiology
1	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
2	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
3	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx