APPENDIX A1- INTERVENTION PROGRAM

Combined Intensive and Consolidation Therapies

Appendix A1 – Intervention Program	Version 1.1
Appendix Date	20 February 2024
Protocol Number	FOR*Ma*T001
Funding	1- Medical Research Future Fund, Australian Government Department of Health 2- Cystic Fibrosis Foundation 3- Anonymous Donor 4- Thoracic Society of Australia and New Zealand 5- The University of Queensland 6- Children's Hospital Foundation
Australian and New Zealand Clinical Trials Registry Number	ACTRN12618001831279
ClinicalTrials.gov Identifier	NCT04310930
EudraCT Number	2020-000050-10
EU-CT Number	2023-506575-99-00-EU CT
Sponsor	The University of Queensland
Contact	FORMaTtrial@uq.edu.au

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

ABBREVIATIONS

AE	Adverse Event
AFB	Acid-Fast Bacilli
ATS	American Thoracic Society
AUC	Area Under the Curve
BAL	Bronchoalveolar Lavage
BAR	Bayesian Adaptive Randomisation
BTS	British Thoracic Society
CEACS	Cost-effectiveness acceptability curves
CF	Cystic Fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CHU9D	Child Health Utility 9D
Cmax	Maximum serum concentration
Cmin	Minimum serum concentration
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DVA	Dynamic Visual Acuity
ECG	Electrocardiogram
eCRF	electronic Case Report Form
FEV1	Forced Expiratory Volume in one second
FOR*Ma*T	Finding the Optimal Regimen for *Mycobacterium abscessus* Treatment
HIT	Head Impulse Test
HRCT	High-Resolution Computed Tomography
HRQoL	Health Related Quality of Life
IA	Inhaled Amikacin
ICD	International Statistical Classification of Diseases

ICERS	Incremental cost-effectiveness ratios
IV	Intravenous
IVA	Intravenous Amikacin
MABS	*Mycobacterium abscessus*
MABS-PD	MABS Pulmonary Disease
MAC	*Mycobacterium avium* Complex
MARS-5	5-item Medication Adherence Rating Scale
MIC	Minimum Inhibitory Concentration
MoOP	Manual of Operating Procedures
MPR	Medication Possession Ratio
NMB	Net Monetary Benefit
NTM	Non-Tuberculous Mycobacteria
PedsQL™	Pediatric Quality of Life Inventory
QALY	Quality-Life Adjusted Years
QoL	Quality of Life
RCT	Randomised Control Trial
REDCap	Research Electronic Data Capture
R-Con	Randomisation – Consolidation
R-PI/IC	Randomisation – Prolonged Intensive/Immediate Consolidation
R-SI	Randomisation – Short Intensive
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-36	Short form-36
SGRQ	St George Respiratory Questionnaire
SOP	Standard Operating Procedure
TDM	Therapeutic Drug Monitoring
TPF	Time Point Final
TPF-PI	Time Point Final – Prolonged Intensive

TPF-SI	Time Point Final – Short Intensive
TPF-WK12	Time Point Final – at Week 12 Visit
TPST	Time Point Start Treatment
TPST-Con	Time Point Start Treatment – Consolidation
TPST-SI	Time Point Start Treatment – Short Intensive
VAS	Visual Analogue Scale
vHIT	Video Head Impulse Test
VOR	Vestibulo-ocular Reflex
WTP	Willingness To Pay
6MWD	Six Minute Walk Distance
6MWT	Six Minute Walk Test

APPENDIX A: INTERVENTION PROGRAM

Appendix A contains the Intervention Program modules, with new modules created as interventions are added to either intensive or consolidation phases of the trial. They are numbered sequentially, A1, A2, A3 etc, with Appendix A1 describing the first iteration of the Intervention Program. The relevant detailed statistical methods and simulations for each Intervention Program module will be described in Appendix F: General Statistical Principles. Separate consent procedures may be required for each appendix. Of note, in some cases data collected as part of one appendix may be incorporated in the analysis of another appendix, if collected to address the same objective. If this occurs, it will be detailed in the relevant appendices. Should an intervention arm be dropped, or a new intervention arm added either to intensive therapy or consolidation therapy this will require a new appendix and a new statistical analysis plan.

Each program in Appendix A will stipulate which of the Discovery studies and Registry linkages is applicable. The Intervention Program modules in Appendix A will include the following:

- A description of the primary and secondary objectives.
- A description of the intervention trial design including any specific inclusion or exclusion criteria specific to the Intervention Program modules.
- A description of the interventions and dosing.
- The methods for assigning treatment arms to the Intervention Program participants.
- Consent requirements.
- Specific Intervention Program trial procedures, monitoring and safety requirements and schedule of assessments.
- A description of relevant nested studies.
- A description of cost effectiveness methodology and analysis as appropriate will be detailed in Appendix E: Health Economics.
- A description of statistical analyses and simulations will be detailed in Appendix F: General Statistical Principles.
- The Discovery studies applicable to the module (if relevant).

APPENDIX A1 – COMBINED INTENSIVE AND CONSOLIDATION MODULE

Appendix A1 describes the initial *Mycobacterium abscessus* Pulmonary Disease (MABS-PD) intervention platform for the FOR*Ma*T trial. Within Appendix A1 there are intensive and consolidation therapy nested studies which are governed by the trial design and conduct described below.

<table>
<tr><th colspan="4">FORMaT Appendix A1 Summary</th></tr>
<tr><td rowspan="2">Treatment combinations:</td><td colspan="3">Intensive therapy arms:</td></tr>
<tr><td>Arm A</td><td>Arm B</td><td>Arm C</td></tr>
<tr><td rowspan="4"></td><td>1. IV amikacin, and;
2. IV tigecycline, and;
3. IV imipenem or IV cefoxitin, and;
4. Oral azithromycin or oral clarithromycin, and;
5. Oral clofazimine.</td><td>1. Inhaled amikacin, and;
2. IV tigecycline, and;
3. IV imipenem or IV cefoxitin, and;
4. Oral azithromycin or oral clarithromycin, and;
5. Oral clofazimine.</td><td>1. IV amikacin, and;
2. IV tigecycline, and;
3. IV imipenem or IV cefoxitin, and;
4. Oral azithromycin or oral clarithromycin.</td></tr>
<tr><td colspan="3">Consolidation therapy arms:</td></tr>
<tr><td colspan="2">Arm a</td><td>Arm b</td></tr>
<tr><td colspan="2">1. Oral clofazimine, and;
2. Oral azithromycin or clarithromycin, and;
3. In combination with one to three of the following oral antibiotics:
• Linezolid,
• Trimethoprim / sulfamethoxazole (co-trimoxazole),
• Bedaquiline,
• Rifabutin.
• Doxycycline
• Moxifloxacin</td><td>1. Inhaled amikacin
2. Oral clofazimine, and
3. Oral azithromycin or clarithromycin, and;
4. In combination with one to three of the following oral antibiotics:
• Linezolid,
• Trimethoprim / sulfamethoxazole (co-trimoxazole),
• Bedaquiline,
• Rifabutin.
• Doxycycline
• Moxifloxacin</td></tr>
<tr><td></td><td colspan="3">A mixed Non-Tuberculous Mycobacteria (NTM) infection (slow grower + Mycobacterium abscessus (MABS)) can include the use of ethambutol in either/both the intensive or consolidation phase/s of treatment.</td></tr>
<tr><td>Appendix A1-specific eligibility:</td><td colspan="3">Inclusion and exclusion criteria as per Master Protocol section 4.1 and below.</td></tr>
<tr><td>Appendix A1-specific inclusions:</td><td colspan="3">1. Positive MABS-PD diagnosis meeting all three American Thoracic Society (ATS) clinical, radiological and microbiological diagnostic criteria for MABS-PD. Defined as;
Clinical: Pulmonary symptoms and exclusion of other diagnoses.
Radiological: Nodular or cavitary opacities on chest radiograph or a chest high-resolution computed tomography (HRCT) scan showing multifocal bronchiectasis with multiple small nodules.
Microbiological: MABS positive culture results from at least two separate expectorated sputum samples.
or;
Positive culture results from at least one bronchial wash or lavage.
or;</td></tr>
</table>

FOR*Ma*T Appendix A1 Summary	
	Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or acid-fast bacilli (AFB)) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washes that are culture positive for NTM. 2. Male or female participants of any age. 3. Informed consent signed by participant or parent/legal guardian if participant is under 18 years of age. For those participating in both the intensive and consolidation modules a combined consent form may be used. 4. Participant has not received MABS-PD treatment in the 12 months preceding assessment of eligibility (this includes drugs prescribed for treatment of other mycobacteria and/or other indications that may have activity against MABS as specified in FOR*Ma*T Prohibited Drug List SOP). 5. Ability to comply with study visits, therapies and study procedures as judged by the site investigator.
Appendix A1-specific exclusions:	1. Participants receiving current treatment for MABS within the previous 12 months (this includes drugs prescribed for treatment of other mycobacteria and/or other indications that may have activity against MABS, as specified in FOR*Ma*T Prohibited Drug List SOP), except for participants taking azithromycin as part of routine treatment for Cystic Fibrosis (CF) or chronic infection-related pulmonary disease). 2. Positive pregnancy test at screening or any time during the FOR*Ma*T trial for females of childbearing potential. 3. Breast-feeding. 4. An unwillingness to comply with the acceptable methods of contraception defined in the relevant section of Appendix A1. 5. QTc>500 milliseconds (QT interval to be corrected based on Fridericia method). 6. Known hypersensitivity to any of the therapies for which no alternative option(s) have been provided.
Target recruitment:	300 participants
Outcome measures:	***Primary outcome:*** MABS clearance from respiratory sample(s) with tolerance at the Final Outcome. ***Secondary outcomes:*** 1. Probability of MABS clearance at Final Outcome irrespective of toxicity according to participant's treatment pathway. 2. Safety of treatment combinations, including changes in microbiological resistance. 3. Change in FEV1 z-score at Final Outcome compared with Screening in participants who do and do not clear MABS at Final Outcome. 4. Phenotype of the structural abnormalities of chest CTs and changes in chest CT scores between Screening and Final Outcome between participants who clear or do not clear MABS at Final Outcome. 5. Predictive value of structural abnormalities on Screening CT scans for sputum conversion and for progression of structural changes in relation to treatment. 6. Change in 6-minute walk distance (6MWD) for adult participants from Screening to Final Outcome according to treatment pathway and in participants who do and do not clear MABS at Final Outcome. 7. Change in HRQoL for participants from Screening to Final Outcome according to treatment pathway and in participants who do and do not clear MABS at Final Outcome. 8. Cost effectiveness of the treatment combinations across intensive and consolidation phases of the trial.

FOR*Ma*T Appendix A1 Summary		
	9. Causes for early withdrawal from MABS-PD treatment due to reasons other than poor tolerance as defined in the primary objectives. ***Exploratory outcomes:*** 1. Participant's MABS clearance status 12 months after Final Outcome.	
Timepoints:	***Screening:***	Up to Minus 42 days from Date of Randomisation-Short Intensive (R-SI).
	Time Point Start Treatment-Short Intensive (TPST-SI):	R-SI.
	Time Point Final (TPF):	End of treatment plus four weeks off-treatment (Final Outcome Visit date).
Nested studies	***Intensive Therapy Modules:***	
	Nested study A1.1:	Type of Short intensive Therapy
	Nested study A1.2:	Duration of intensive therapy for patients completing short intensive treatment with ongoing positive MABS cultures collected at 4 weeks and randomised to either a further 6 weeks intensive therapy or immediate consolidation.
	Consolidation Therapy Module:	
	Nested study A1.3:	The use of oral therapy only or oral therapy and inhaled amikacin for consolidation therapy.

Intensive Therapy Module Nested Studies		
Nested study A1.1: Type of Short Intensive Therapy		
Timepoints:	***Screening:***	Up to Minus 42 days from Date of R-SI.
	TPST-SI:	R-SI
	Time Point Final-Short Intensive (TPF-SI)*:	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.
	*The most accurate method of determining TPF for this trial phase is calculating the time immediately preceding randomisation to the next treatment phase i.e. date of next randomisation minus 1 day.	
Nested study A1.2: Duration of intensive therapy for patients with ongoing positive MABS cultures		
Timepoints:	***Screening:***	Up to Minus 42 days from R-SI.
	TPST-SI:	Date of R-SI
	TPF-PI* or TPF-WK12:	Date of R-Con minus 1 day (for those allocated to prolonged intensive) or Week 12 visit date (for those allocated to immediate consolidation).
	*The most accurate method of determining TPF for this trial phase is calculating the time immediately preceding randomisation to the next treatment phase i.e. date of next randomisation minus 1 day.	

Consolidation Therapy Module Nested Study		
Nested study A1.3: Use of oral therapy +/- inhaled amikacin for consolidation therapy		
Timepoints:	***Time Point Start Treatment-Consolidation (TPST-Con):***	Date of R-Con
	TPF:	End of treatment plus 4 weeks off treatment (Final Outcome Visit date).

1 INTRODUCTION

The probability of microbiological clearance with acceptable toxicity for treatment combinations tested in FOR*Ma*T, inclusive of both Appendix A1 intensive and Appendix A1 consolidation for patients with *Mycobacterium abscessus* pulmonary disease (MABS-PD) will be determined.

The probability of microbiological clearance with acceptable toxicity of treatment combinations will also be examined in different patient subpopulations (CF and non-CF, those infected with different MABS subspecies (*M. a. abscessus/ M. a. bolletii* [inducible macrolide resistance] and *M. a. massiliense)* and those with constitutive macrolide resistance and those with mixed NTM infections).

The best therapy combinations may then form the control arms for new intervention studies which can be added as new arms within Appendix A.

Sites may undertake both intensive and consolidation modules or if they are unable to conduct the intensive therapy module, then they can partner with a FOR*Ma*T site that is able to manage the intensive therapy module, and only undertake the consolidation module themselves. Sites that are unable to undertake the intensive therapy module themselves and are unable to partner with a site that is able to manage the intensive therapy module, can choose to only undertake the consolidation module (see Appendix A2 for detailed information).

2 OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objective for Appendix A1 is to determine the optimal treatment for MABS-PD. Optimal treatment is defined by MABS clearance from respiratory samples with tolerance at 56 weeks (denoted Final Outcome) for participants who received short intensive therapy or at 62 weeks (denoted Final Outcome) for participants who received prolonged intensive therapy.

Definition of tolerance:

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.

MABS clearance at final outcome will be defined as:

Negative MABS cultures from four consecutive sputum samples with one of those sputum specimens collected four weeks after the completion of consolidation therapy (either week 56 or 62, depending on treatment arm randomisation). Or, a MABS negative Bronchoalveolar Lavage (BAL) collected four weeks after completion of consolidation (either week 56 or 62, depending on treatment arm randomisation).

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 examine the change in Forced Expiratory Volume in one second (FEV1) z-score at Final Outcome compared with Screening in patients 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 between those who clear and those who do not clear MABS at Final Outcome.
5. To examine the predictive value of structural abnormalities on Screening CTs for sputum conversion and for progression of structural changes in relation to therapy.
6. 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 MABS at Final Outcome.
7. To examine 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 examine general HRQoL 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.

2.3 EXPLORATORY OBJECTIVES

- To examine MABS clearance status at twelve (12) months after Final Outcome.

3 DESIGN

Appendix A1 describes the intensive and consolidation modules (Figure A1.1) and will test therapies that are currently used and are the basis for the current treatment guidelines.

The intensive and consolidation modules function as nested studies within the trial.

Sites that are unable to participate in intensive therapy (nested A1 studies A1.1 and A1.2) but are able to undertake consolidation (nested study A1.3) may still be included as a trial site and partner with other trial sites that are able to undertake intensive therapy to facilitate trial participation (see FOR*Ma*T Shared Trial Sites SOP for further information on management of shared trial sites).

Intensive Therapy Module

Appendix A1.1: Short Intensive Therapy:

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

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

Appendix A1.2: Duration of Intensive Therapy for Patients with Ongoing Positive MABS cultures after completing 4 weeks vs 10 weeks of Intensive Therapy.

Consolidation Therapy Module

Appendix A1.3: The use of oral therapy only or oral therapy and inhaled amikacin for Consolidation Therapy. Note, participants recruited as part of Appendix A2 will also be included in the analysis of the objectives of this nested study.

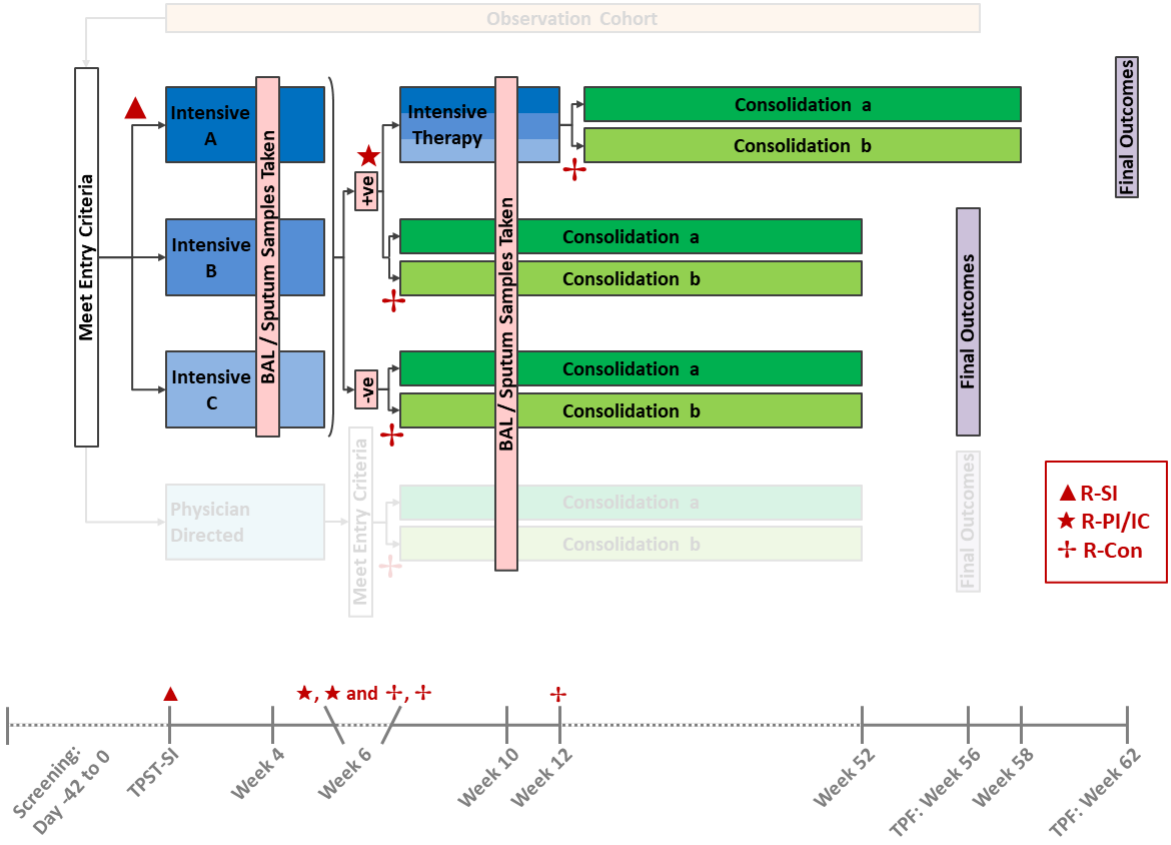

Figure 1 Flow Diagram for Appendix A1, Intervention Program Eligibility into the Intervention Program is determined at screening. At Randomisation-Short Intensive (R-SI) (▲); participants are randomised between the different intensive therapy arms (Intensive A, Intensive B and Intensive C) for a period of 6 weeks. At the end of intensive therapy, it will be determined if participants are still MABS positive, or MABS negative (cleared). Randomisation-Prolonged Intensive or Immediate Consolidation (R-PI/IC) (★) will ONLY be for participants who are still MABS positive based on respiratory samples taken at 4 weeks and will allocate participants to either 1) continue intensive therapy or 2) immediately commence consolidation therapy. Randomisation-Consolidation (R-Con) (✢) allocates participants to the consolidation therapy arms either at week 6 (for those allocated to immediate consolidation) or at week 12 (for those allocated to prolonged intensive therapy). Refer to Appendix A2 for information regarding Consolidation Only intervention program module where participants receive physician directed intensive therapy prior to enrolment into Consolidation Only program.

4 ELIGIBILITY CRITERIA

Participants are eligible for Appendix A1 if the following criteria are met:

4.1 INCLUSION CRITERIA

1. Positive MABS-PD diagnosis meeting all three American Thoracic Society clinical, radiological and microbiological diagnostic criteria for MABS-PD. Defined as:

   Clinical: Pulmonary symptoms and exclusion of other diagnoses.

   Radiological: Nodular or cavitary opacities on chest radiograph or a chest high-resolution computed tomography (HRCT) scan showing multifocal bronchiectasis with multiple small nodules.

   Microbiological: MABS positive culture results from at least two separate expectorated sputum samples.

or

Positive culture results from at least one bronchial wash or lavage.

or

Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or acid-fast bacilli, (AFB))) and positive culture for NTM ***or*** biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washes that are culture positive for NTM.

2. Male or female participants of any age.
3. Informed consent signed by participant or parent/legal guardian if participant is under 18 years of age. For those participating in both the intensive and consolidation modules at the same site a combined consent may be used. For those sites only participating in the consolidation module, a specific consolidation consent may be required.
4. Participant has not received MABS-PD treatment in the 12 months preceding assessment of eligibility (this includes drugs prescribed for the treatment of other mycobacteria and/or other indications that may have activity against MABS, as specified in FOR*Ma*T Prohibited Drug List SOP).
5. Ability to comply with study visits, therapies and study procedures as judged by the site investigator.

4.2 EXCLUSION CRITERIA

- Participants receiving treatment for MABS within the previous 12 months (this includes drugs prescribed for treatment of other mycobacteria and/or other indications that may have activity against MABS, as specified in FOR*Ma*T Prohibited Drug List SOP), except for participants taking azithromycin as part of routine treatment for CF or chronic infection-related pulmonary disease.
- Positive pregnancy test at any time during the FOR*Ma*T trial for females of childbearing potential.
- Breast-feeding.
- An unwillingness to comply with the acceptable methods of contraception, as described in Section 5 of this appendix.
- Participants with a QTc interval >500 milliseconds (QT interval corrected based on Fridericia method).
- Known hypersensitivity to any of the therapies for which no alternative option(s) have been provided. This includes:
    - Amikacin,
    - Tigecycline,
    - Macrolide antibiotics, and
    - Clofazimine.

4.3 ADDITIONAL CRITERIA

4.3.1 MIXED NTM INFECTIONS

Participants who have cultured slow growing NTM of the same species two or more times in the 24 months prior to screening, with one of those cultures within the 6 months prior to screening will be considered to have mixed NTM infection at the time of screening. If the participant meets all other inclusion criteria and no exclusion criteria they will be eligible for participation. Ethambutol may be used in addition to trial therapies to cover mixed infections considered to require treatment by their clinician.

4.3.2 CO-ENROLMENT WITH OTHER TRIALS

Co-enrolment is not permitted when there is a potential interaction between trial interventions, any compromise to the validity of either trial or impact on participants' rights and/or safety. However, co-enrolment may be permitted in the instance where all trials that the participant is enrolled or to be enrolled in have mutually agreed to the co-enrolment arrangement.

5 ACCEPTABLE METHODS OF CONTRACEPTION

The effects of some drugs used during the Intervention Program on the unborn child and on the newborn baby are not known. Because of this, it is important that participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project.

It is therefore important that highly effective birth control is used while in this study. Site investigators should discuss effective methods of contraception with participants. Both male and female participants are to use effective contraception, used correctly with every act of sexual intercourse, from at least 14 days before the first dose of MABS-PD therapy, during the course of the trial and for a period of 90 days after the last dose of MABS-PD therapy. Acceptable methods of contraception for participants enrolled in Appendix A1 include:

1) Male vasectomy 6 months or more previously, with a documented negative post-vasectomy semen analysis for sperm.
2) Female bilateral tubal ligation performed at least 6 months previously.
3) Female continuous use of an intrauterine device (non-hormone releasing or hormone releasing) for at least 90 days before the first dose of MABS-PD therapy.
4) Female combined (estrogen and progestogen-containing) or progestogen-only oral, injected, implanted or vaginal hormonal contraception associated with inhibition of ovulation.

The barrier contraception methods listed below are not acceptable and are only to be used in special circumstances where the investigator determines that barrier contraception is appropriate.

1) Male and female condom with spermicide (either as a single product if commercially available and/or as allowed according to local regulations; otherwise condom and spermicide as separate products).
2) Male condom with female diaphragm, cervical cap, or vaginal sponge, each with spermicide.

For female participants using birth control pills

The use of birth control pills for contraception must be discussed and approved by the local site investigator at the start of each phase of the trial and when any changes in therapy occur, as some therapies used during the trial may interact with the effectiveness of birth control pills. Birth control pills should be in successful use from at least 60 days before the first dose of MABS-PD therapy (unless otherwise noted) and until 90 days following the last dose of MABS-PD therapy.

Female participants who change their method of contraception to birth control pills during the trial must continue to use a second form of approved contraception for at least 60 days after starting the use of birth control pills.

For female participants using hormonal injected, implanted or vaginal contraception

Injected, implanted or vaginal hormonal contraception should be used successfully from at least 60 days before the first dose of MABS-PD therapy (unless otherwise noted) and until 90 days following the last dose of MABS-PD therapy.

6 TRIAL CONDUCT

6.1 INFORMED CONSENT

In addition to providing consent to the FOR*Ma*T Master Protocol, participants enrolling in the Intervention Program are required to sign and date the relevant Appendix A1 consent. Consent to Appendix A1 includes consent to all Appendix A1 nested studies. Consent will be obtained from participants or their parent/guardian in accordance with the policies described in section 5.4 of the FOR*Ma*T Master Protocol.

6.2 PREGNANCY INFORMATION CONSENT

If a FOR*Ma*T trial participant becomes pregnant or is the biological father of a child conceived while enrolled in this Intervention Program the site investigators are requested to provide the participant with the FOR*Ma*T pregnancy information and consent form. The FOR*Ma*T pregnancy and consent form requests to follow the participant and the child for 12 months after conception. Please refer to FOR*Ma*T Safety Monitoring and Reporting SOP for further detail for safety monitoring and reporting of pregnancies and pregnancy outcomes in female trial participants or female partners who are pregnant to male participants in the Intervention Program.

6.3 METHODS OF ASSIGNING PARTICIPANTS TO TREATMENT ARMS

Participants will be randomised into different treatment arms for both the intensive and consolidation phase of treatment as described in the Master Protocol section 6.2 using the randomisation technique minimisation, initially in a 1:1:1 ratio for R-SI and 1:1 ratio for R-PI and R-Con. As described in the Master Protocol, all randomisations will be conducted via Research Electronic Data Capture (REDCap) at each FOR*Ma*T trial site. At each stage, study staff will enter the subject demographic data and the stratification factors (see section 6.3 in the Master Protocol) into REDCap, which will then inform them of the participant's treatment allocation for that stage.

Following interim analysis, after 60 participants have completed 6 weeks of intensive therapy, if appropriate, Bayesian Adaptive Randomisation (BAR) will be implemented for R-SI to implement the allocation probabilities which will be used until the data support either early stopping for futility, or a maximum sample size is attained. Refer to Appendix F: General Statistical Principles for detailed information regarding randomisation and statistical principles for Appendix A1.

7 INTERVENTION PROGRAM PROCEDURES AND SAFETY MONITORING

In addition to the core trial procedures described in the Master Protocol, participants enrolled in the Intervention Program are required to undertake procedures and regular toxicology monitoring. The type of toxicology monitoring procedure required will be determined by the treatment arm the participant is allocated to, and in accordance with the schedule of assessments outlined in tables 12 to 14. Toxicology thresholds will be defined in accordance with CTCAE criteria as outlined in the Master Protocol, section 5.9.2. The outcome of all the assessments below will be documented in the corresponding Case Report Form (CRF) and entered into REDCap.

7.1 SERUM/URINE PREGNANCY TEST

All female participants of childbearing potential are required to undergo regular pregnancy testing while enrolled in the Intervention Program. Childbearing potential is defined as a premenopausal female capable of becoming pregnant, and includes females on oral, injectable, or mechanical contraception; females who are single and females whose male partners have been vasectomised or are using mechanical contraception (1). A serum pregnancy test will be performed at screening and at the final study visit (either week 56 or 62 depending on treatment arm allocation) and if applicable, at the early withdrawal visit. A urine β-hCG test or serum pregnancy is acceptable for regular pregnancy monitoring from day 1 in accordance with the schedule of assessments outlined in tables 12 to 14. Both urine and serum pregnancy tests are to be performed in accordance with site specific procedures.

7.2 CHEST CT SCAN

The chest CT scan for screening is to be performed ideally within the three months prior to screening for Intervention Program participants (maximum of six months earlier).

7.3 RESPIRATORY SAMPLING

For screening a minimum of 2 sputum samples (with at least 1 collected within 6 months prior to screening and other samples collected within 12 months prior to screening) or 1 BAL collected within 6 months prior to screening is required for Intervention Program participants. Tables 12 to 14 outline the minimum respiratory sample collection timepoints during the trial; however, monthly sputum sample collections are recommended.

7.4 AUDIOGRAM

To monitor aminoglycoside induced ototoxicity, regular audiometry assessments will be undertaken in accordance with the schedule of assessments outlined in tables 12 to 14. The battery of assessments to be completed should comply with the site-specific requirements. Assessments can be conducted in either a hospital or community setting.

7.5 VESTIBULAR MONITORING

Vestibular toxicity monitoring will document any vestibular symptoms (motion-induced oscillopsia, postural instability and gait unsteadiness) associated with prolonged aminoglycoside use. Assessments will take place in accordance with the schedule of assessments outlined in tables 12 to 14. Testing can be completed either by the treating physician or a physiotherapist. Additional vestibular monitoring may be required if deemed necessary by the Site investigator.

7.5.1 DYNAMIC VISUAL ACUITY TESTING (DVA)

Ask the patient to read a visual acuity chart (e.g., Snellen) while sitting still at recommended distance. This result is their static visual acuity. Repeat task while oscillating the patient's head horizontally or vertically at 1 to 2 Hz. An abnormal DVA is defined as loss of at least three lines of visual acuity compared with static condition (horizontal and/or vertical).

7.5.2 HEAD IMPULSE TESTING (HIT)

Stand in front of the seated patient, facing them, and ask the patient to focus on a target directly in front of them. Briskly rotate the patient's head horizontally approximately 10 to 20° amplitude, watching the patient's eyes closely. In normal subjects, the patient's eyes remain still as they remain on target. However, in a patient with impaired vestibulo-ocular reflex (VOR), the patient's eyes drift off the target and require a corrective 'catch-up' saccade to re-fixate on the target and stabilise vision. This catch-up saccade is a small amplitude horizontal eye movement in the opposite direction of the head turn and should occur with every head impulse (repeatable).

If available, Video Head Impulse Test (vHIT) is recommended as this has a higher sensitivity than the traditional bedside head impulse test at detecting impaired VOR. M=The main benefits include detecting covert (hidden) catch up saccades and peer review.

7.5.3 ROMBERG ON FOAM TEST

On a foam surface, ask the participant to stand still with two feet together. The participant should be able to stand steady with their eyes open. If the participant is not able to perform this task, ask them to separate their feet to minimal distance that allows them to do so. Repeat the task this time with their eyes closed. Record if the participant falls (positive Romberg test) or does not (negative Romberg test).

Document vestibular test results and any further actions (if results indicate significant vestibular impairment) in the CRF.

7.6 PHYSICAL EXAMINATION

The physical examination will be performed in accordance with the procedures outlined in the FOR*Ma*T Master Protocol, section 5.5.5. in accordance with the schedule of assessments outlined in tables 12 to 14.

7.7 ELECTROCARDIOGRAM (ECG)

A standard 12 lead ECG will be performed in accordance with the relevant tables and site-specific procedures after the participant has been supine for at least 5 minutes. A site investigator will interpret, sign and date the ECG. The

QTc interval and the clinical interpretation will be recorded in the electronic case report form (eCRF) and ECGs will be required to be scanned and stored in the CRF. The QT interval at Screening is to be corrected using the Fridericia method. For any subsequent QTc intervals which are 'abnormal' the Fridericia method is to be used to confirm the QTc value.

7.8 SIX-MINUTE WALK TEST

A 6-minute walk test (6MWT) will be performed in adult participants only, at the time points outlined in tables 12 to 14 if the testing is available at the trial site. The 6MWT will be performed according to the protocol in the ATS Statement: Guidelines for the Six Minute Walk Test (2) and/or local standard procedures. Results of the 6MWT will be recorded in the relevant eCRF in the FOR*Ma*T database by the end of the Final Outcome visit.

7.9 BLOOD SAMPLING

Blood samples will be collected in accordance with tables 12 to 14. Liver function, full blood count and chemistry and renal function tests (refer to FOR*Ma*T Monitoring Blood Parameters SOP for specific blood parameters to be measured) are to be performed in accordance with the local pathology requirements. All relevant de-identified blood pathology reports are to be uploaded in the appropriate eCRFs in the FOR*Ma*T database by the end of the Week 6, Week 12 and Final Outcome Visits. Any blood abnormalities that meet Adverse Event (AE) or Serious Adverse Event (SAE) criteria are to be reported as an AE/SAE within the specified timeframes.

7.10 STUDY MEDICATION REVIEW

Participant adherence to MABS-PD treatment in the intervention cohort will be measured via two indirect methods. Self-reported adherence will be assessed using a questionnaire, the 5-item Medication Adherence Rating Scale (MARS-5)(3, 4) at the timepoints outlined in tables 12 to 14 and results recorded in the Medication Adherence Questionnaire CRF. Data from pharmacy prescription refill records and prescription claims databases will be obtained (where possible) and used to calculate the refill adherence measure, Medication Possession Ratio (MPR) (5-8).

7.11 AMIKACIN ADMINISTRATION AND MONITORING

7.11.1 NEBULISER TYPE FOR IA

Amikacin for injection preparation (not liposomal amikacin) is to be used for inhalation in participants randomised to inhaled amikacin. A low preservative preparation, if available, is advised to reduce the risks of bronchospasm. The brand of amikacin preparation, if known, is to be recorded in the study drug CRF. Five hundred milligrams of amikacin should be administered according to local standard practices. Prior to administration the patient should receive a bronchodilator, for example salbutamol, to reduce the risk of coughing and bronchospasm. This can be given nebulised or by metered dose inhaler. Amikacin for injection may only be mixed with sodium chloride 0.9%. It must not be nebulised as a mixture with other nebulised drugs (e.g. salbutamol, dornase alfa or other nebulised antibiotics).

High efficiency nebulisers are required to nebulise amikacin (IV formulation). A suitable nebuliser with a filter attachment (e.g., SideStream Plus with filter attachment, or Pari LC Plus with filter attachment) are to be used to

prevent environmental deposition of nebulised antibiotics and to reduce the risk of developing antibiotic resistant organisms. Air flow of 6-10 L/min is required to achieve effective nebulisation of amikacin.

7.11.2 AMIKACIN THERAPEUTIC DRUG MONITORING

TDM of intravenous amikacin will be required to reduce and monitor toxicity. There is currently variation across trial sites surrounding amikacin TDM methods. To reflect this, acceptable amikacin TDM strategies that can be used in this trial include;

1) Trough amikacin levels (independent of minimum inhibitory concentration (MIC) using nomogram for next dose);
2) Maximum serum concentration (C_{max})/MIC target;
3) Area under the curve (AUC) target;
4) C_{max}/MIC and minimum serum concentration (C_{min});
5) AUC/MIC and C_{min}.

The chosen amikacin TDM strategy used must be recorded in the CRF and adhered to consistently for that participant.

For subjects randomised to Intensive Therapy Arm B, an amikacin level should be collected at week one, 90 minutes (range 60 to 120 minutes) post completion of the inhaled dose. The time of starting and completing the inhaled therapy and time of blood collection should be documented. No adjustment of the inhaled amikacin dose should be undertaken.

7.12 HEALTH RELATED QUALITY OF LIFE AND UTILITY MEASURES

HRQoL will be assessed in all participants (where possible) according to the schedule of assessments in the relevant appendix. The questionnaires are required to be completed prior to any clinical assessment and are dependent on the participant's age and whether they have CF. The age appropriate HRQoL questionnaire issued to the participant at the start of the study will continue to be used throughout the study even if the participant progresses to a different age range. HRQoL questionnaires will be made available to study sites. All questionnaires will be made available in English or if available the local language version will be sourced. Questionnaires can be completed by the participant and/or their parent/carer via an online link to the questionnaire(s) on the trial database or if unable to access the electronic form these may be completed using a paper-based questionnaire. Responses from paper-based questionnaires are to be entered into the trial database by trial site staff.

7.12.1 CYSTIC FIBROSIS QUESTIONNAIRE-REVISED (CFQ-R)

The CFQ-R has been developed specifically for use in people with CF. This questionnaire measures the impact of CF on overall health, daily life, perceived well-being and symptoms. Age-appropriate questionnaires have been developed; CFQ-R teen/adult for adolescents and adults 14 years of age and older, the CFQ-R child for those 6-13 years of age, and the CFQ-R parent for the parents of those aged 6-13.

In children ≤16 years of age, the CFQ-R should be administered after the PedsQL™.

7.12.2 EQ-5D-5L

The EQ-5D-5L questionnaire is a standardised measure of health status in adults 18 years of age and older. This questionnaire can be applied as a generic measure of health for clinical and economic appraisal, including the calculation of quality-life adjusted years (QALYs). The EQ-5D-5L measures five dimensions:

1. Mobility;
2. Self-care;
3. Usual activities;
4. Pain/discomfort;
5. Anxiety/depression.

Each dimension has five possible answers: no problems, slight problems, moderate problems, severe problems and extreme problems. The respondent is asked to indicate his/her health state by selecting the most appropriate statement from a list.

7.12.3 EQ-5D-Y

The EQ-5D-Y is the child friendly version of the EQ-5D-5L questionnaire. The EQ-5D-Y has been developed for use in children 8 to 17 years of age. The dimensions and the visual analogue scale (VAS) measured are the same as the EQ-5D-5L questionnaire, but with child friendly wording. For children 4 to 7 years of age the proxy 1 version of the EQ-5D-Y can be utilised allowing the respondent (parent/carer) to evaluate participants quality of life (QoL) from respondents' own view.

7.12.4 ST. GEORGE RESPIRATORY QUESTIONNAIRE (SGRQ)

The SGRQ is to be completed by all non-CF participants 18 years of age and older. The SGRQ is a supervised self-administered 50-item questionnaire measuring health status across three domains: symptoms, activity and impacts (psycho-social) in people with airway obstruction.

7.12.5 SHORT FORM- 36 HEALTH SURVEY

The SF-36 health survey is a self-reported questionnaire applicable in all participants 16 years and older. Covering eight health concepts the SF-36 health survey is a generic outcome measure designed to examine a person's perceived health status.

7.12.6 PEDIATRIC QUALITY OF LIFE INVENTORY (PEDSQL™)

The PedsQL™ child health questionnaire is a non-preference-based measure to assess HRQoL for children and adolescents from 2 years up to 16 years of age. Children less than 16 years of age at screening will continue to use the PedsQL™ up until the end of the trial, rather than change to using the SF-36 if they turn 16 years of age during the study.

Developmentally appropriate child self-report questionnaires are available (ages 5-7, 8-12, 13-18) together with parent/carer proxy-reports (ages 2-4, 5-7, 8-12 and 13-18). If feasible, the PedsQL™ should be completed *before* the respondents complete any other health data forms and *before* they see their physician or healthcare provider.

Parents/carers, children (aged 8-12) and young people (aged >12 years) may self-administer the PedsQL™ after the FOR*Ma*T site researcher has provided instructions. If it is determined by the FOR*Ma*T site researcher that the child, young person or parent/carer is unable to self-administer the PedsQL™ the questionnaire should be administered, word for word by the FOR*Ma*T site researcher. If the child has difficulty understanding the age appropriate PedsQL™ the preceding age questionnaire may be used. The parent and the child must complete the questionnaires independently of each other and in accordance with the PedsQL™ administration guidelines (available via hyperlink or refer to relevant section in FOR*Ma*T Trial Site Manual of Operating Procedures (MoOP)).

7.12.7 CHILD HEALTH UTILITY 9D (CHU9D)

The CHU9D is a generic preference-based measure of paediatric HRQoL for use in children 7 to 17 years of age. The use of a descriptive system and a set of preference weights allows for the calculation of quality adjusted life years (QALYs) for use in economic evaluation.

7.13 MABS CLEARANCE FOLLOW-UP QUESTIONNAIRE

Site investigators will be requested to complete a follow up questionnaire for eligible intervention participants to assess microbiological clearance of MABS at 12 months after final outcome.

8 SITE REIMBURSEMENT

For participants enrolled in Appendix A1, trial sites will be reimbursed on a per participant basis at each of the following time points;

1. Screening;
2. End of intensive;
3. End of consolidation;
4. Final study visit.

Sites will be reimbursed according to their contract. Payments will be paid for each time point once the data is entered into the trial database and all queries finalised. Invoices should be prepared at a minimum of every 6 months.

9 INTENSIVE THERAPY NESTED STUDIES

9.1 NESTED STUDY A1.1: SHORT INTENSIVE THERAPY

9.1.1 PRIMARY OBJECTIVE

To compare the efficacy of intensive therapies on microbiological clearance of MABS with good tolerance at end of short intensive. Respiratory samples will be collected at 4 weeks to allow microbiological outcomes to be available at end of short intensive and tolerance will be assessed at the end of short intensive. Treatment will continue up until the end of short intensive (6 weeks). Specifically, the effects of inhaled amikacin (IA) versus intravenous amikacin (IVA) will be examined (A1.1.1) and the efficacy of additional oral clofazimine to standard intravenous therapy will be examined (A1.1.2).

Investigation of the efficacy of intensive therapy on microbiological clearance with acceptable toxicity of treatment combinations will also be examined in different patient subpopulations (CF and non-CF, those infected with different MABS subspecies *M. a. abscessus/ M. a. bolletii* [inducible macrolide resistance] and *M. a. massiliense*) and those with constitutive macrolide resistance).

MABS clearance at the end of the short intensive therapy will be defined as negative MABS cultures from all 3 sputum samples or from one BAL sample collected at week 4.

Additional studies nested within Appendix A1.1 are:

A1.1.1: Use of IA During Intensive Therapy to Replace IVA in the Treatment of MABS-PD;

A1.1.2: The use of Additional Clofazimine to Standard IV Therapies During Intensive Therapy in the Treatment of MABS-PD.

9.1.1.1. Study A1.1.1: Use of Inhaled Amikacin (IA) During Intensive Therapy to Replace Intravenous Amikacin (IVA) in the Treatment of MABS-PD

Introduction

Amikacin is an aminoglycoside recommended in guideline-based therapy for the treatment of MABS-PD. It can be administered either intravenously or nebulised for inhalation (using the IV formulation). Inhaled aminoglycosides have the potential advantages of achieving higher airway concentrations, while reducing the risk of systemic toxicity. However, amikacin for inhalation is not currently available commercially for the indication of treating MABS and clinicians have used an "off-label" IV form of amikacin (delivered via a nebuliser). A Phase II Randomised Control Trial (RCT) (9) of amikacin liposome inhalation suspension (Arikayce) sponsored by Insmed Inc., investigated the safety and efficacy of Arikayce to treat NTM infection (36% MABS) in addition to highly variable multi-drug therapy in 89 patients with (19%) and without (81%) CF in patients who had failed to clear infection using their current treatment. The trial did not meet the primary endpoint of decreased mycobacterial load, but the treatment group had a higher proportion of subjects with >1 negative sputum (32% vs 9%, p=0.006) and improved 6- minute walk distance, suggesting a potential benefit from adding Arikayce to consolidation therapy. Arikayce has now been approved for the treatment of patients infected with *Mycobacterium avium* complex (MAC) who do not respond to conventional treatment. This trial highlighted the difficulties and inefficiencies of undertaking conventional clinical trials using the "one population, one drug, one disease" in a disease where there are relatively small patient numbers, a heterogeneous population and complex, inconsistent drug combinations. These factors greatly limit the clinical information obtained and contribute to making conventional trials in this patient population difficult to interpret. This contrasts with innovative platform trials, which have advantages for efficiently evaluating multiple treatment combinations (e.g. multi-drug resistant TB (10)) requiring complex drug regimens in a heterogeneous population.

Eligibility Criteria

No additional eligibility criteria are required for participation in A1.1.1 from those described in Appendix A1, Section 4.

Objectives

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 between the use of IA (Arm B) and the use of IVA (Arm A) given during intensive phase.

Secondary Objectives

1. Microbiological clearance at 4 weeks (irrespective of toxicity) with use of IA (Arm B) compared with use of IVA (Arm A) in different patient subpopulations (CF and non-CF, those infected with different MABS subspecies M. a. abscessus/ M. a. bolletii [inducible macrolide resistance] and M. a. massiliense and those with constitutive macrolide resistance).
2. Safety of using IA to replace IVA in the short intensive therapy phase.

3. Change in FEV1 z-score at end of short intensive therapy versus at Screening with use of IA (Arm B) compared with use of IVA (Arm A).
4. Change in HRQoL (CFQ-R) for participants at end of short intensive therapy versus at Screening with use of IA (Arm B) compared with use of IVA (Arm A).
5. To examine general HRQoL between Screening and end of short intensive therapy in participants with use of IA (Arm B) compared with use of IVA (Arm A).
6. To examine the cost effectiveness of IA compared with IVA during short intensive therapy.
7. To examine causes for early withdrawal from MABS-PD treatment due to reasons other than poor tolerance as defined in the primary objectives with use of IA (Arm B) compared with use of IVA (Arm A).

Statistical Analysis

Details of the simulations (sample size calculation) for Appendix A1 are outlined in Section 6 of the Master Protocol and the relevant section of Appendix F: General Statistical Principles and the Statistical Analysis Plan (SAP).

9.1.1.2. Study A1.1.2: The Use of Additional Clofazimine to Standard Intravenous Therapies During Intensive Therapy in the Treatment of MABS-PD

Introduction

Clofazimine is approved for use in leprosy. It has recognised antibacterial and anti-inflammatory effects in the management of leprosy and has been used to treat erythema nodosum related to leprosy. There is no current clinical trial evidence to support the use of clofazimine in the treatment of MABS-PD. Clofazimine use has however increased clinically, potentially driven by the difficulty in achieving microbiological clearance and reports of *in vitro* synergy between combinations of clofazimine and amikacin (11, 12).

Eligibility Criteria

No additional eligibility criteria are required for participation in nested study A1.1.2 from those described in Appendix A1, Eligibility Criteria.

Objectives

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 between standard IV therapy without clofazimine (Arm C) and with clofazimine (Arm A) given during intensive phase.

Secondary Objectives

1. Microbiological clearance from respiratory samples collected at 4 weeks with acceptable toxicity of intensive therapy at the end of short intensive therapy without (Arm C) and with the addition of clofazimine (Arm A) to standard IV treatment will be examined in different patient subpopulations (CF and non-CF, those infected with different MABS subspecies M. a. abscessus/ M. a. bolletii [inducible macrolide resistance] and M. a. massiliense) and those with constitutive macrolide resistance).
2. Microbiological clearance (irrespective of toxicity) at 4 weeks without (Arm C) and with the addition of clofazimine (Arm A) to standard IV treatment.
3. Microbiological clearance (irrespective of toxicity) at 4 weeks without (Arm C) and with the addition of clofazimine (Arm A) to standard IV treatment will be examined in different patient subpopulations (CF and non-CF, those infected with different MABS subspecies M. a. abscessus/ M. a. bolletii [inducible macrolide resistance] and M. a. massiliense) and those with constitutive macrolide resistance).
4. Safety of treatment without (Arm C) and with the addition of clofazimine (Arm A) in the short intensive therapy phase.
5. Change in FEV1 z-score between Screening and end of short intensive therapy in participants treated without (Arm C) and with the addition of clofazimine (Arm A).
6. Changes in HRQoL (CFQ-R) for participants with CF between Screening and end of short intensive therapy in participants treated without (Arm C) and with the addition of clofazimine (Arm A).
7. To examine general HRQoL between Screening and end of short intensive therapy in participants treated without (Arm C) and with the addition of clofazimine (Arm A).

8. To examine the cost effectiveness of treatment without (Arm C) and with the addition of clofazimine (Arm A) during short intensive therapy in addition to standard IV treatment.
9. To examine causes for early withdrawal from MABS-PD treatment due to reasons other than poor tolerance as defined in the primary objectives without (Arm C) and with the addition of clofazimine (Arm A) to standard IV treatment.

Statistical Analysis

Details of the sample size calculation for this study are presented in Section 6.0 of the Master Protocol and the relevant section of Appendix F: General Statistical Principles and in the SAP.

9.2 NESTED STUDY A1.2: DURATION OF INTENSIVE THERAPY FOR PATIENTS WITH ONGOING POSITIVE MABS CULTURES AFTER 4 WEEKS OF INTENSIVE THERAPY.

9.2.1 INTRODUCTION

Current published guidelines for the treatment of MABS-PD (13-15) are based on expert opinion, and in practice treatments vary considerably (16). Suggested regimens include an intensive phase of 4-12 weeks of IV antibiotics with duration based on clinical and microbiological response. Whether extending the length of intensive therapy improves microbiological clearance of MABS is not known but the strategy is used clinically in patients with ongoing positive cultures. Toxicity and costs are thought to be related to length of treatment and need to be balanced against the potential for better microbiological outcomes.

9.2.2 ELIGIBILITY CRITERIA

Participants are required to have completed 6 weeks of intensive therapy and will have at least one out of 3 sputum cultures or one BAL culture positive for MABS collected at week 4 (± 3 days).

No other additional eligibility criteria are required for participation in nested study A1.2 from those described in Section 4 of Appendix A1.

9.2.3 OBJECTIVES

9.2.3.1. Primary 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.

MABS clearance, assessed at the end of prolonged intensive therapy (for those allocated to prolonged intensive) or at 12 weeks (for those allocated to immediate consolidation) will be defined as negative MABS cultures from all 3 sputum samples or from one BAL sample collected at 10 weeks.

9.2.3.2. Secondary Objectives

1. To compare microbiological clearance from samples collected at 10 weeks (irrespective of toxicity) in prolonged intensive therapy compared with short intensive and 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 and 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 between those participants still culture positive for MABS at 10 weeks compared with those who have cleared MABS at 10 weeks.

5. 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.

6. 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 and immediate consolidation therapy who had MABS positive cultures from samples collected at 4 weeks.

7. Changes in general HRQoL in prolonged intensive therapy compared with short intensive and immediate consolidation therapy in patients who had MABS positive cultures at 4 weeks.
8. Change in CT scan parameters (bronchiectasis, mucus plugging, airway wall thickening, --atelectasis, % disease and air trapping), between Screening and end of prolonged intensive therapy (for those allocated to prolonged intensive) or 12 weeks (for those allocated to immediate consolidation) taking into account microbiological clearance based on samples collected at 4 and at 10 weeks.
9. To examine the cost effectiveness of prolonged intensive compared with short intensive and immediate consolidation for those who remain MABS positive based on samples collected at 4 weeks.
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.

9.2.4 STATISTICAL ANALYSIS

Details of the sample size calculation for this study are presented in Section 6.0 of the Master Protocol and the relevant section of Appendix F: General Statistical Principles and in the SAP.

9.3 INTENSIVE THERAPY DOSING REGIMEN

At R-SI, participants will be randomised to one of three treatment arms during the intensive phase and will receive drug therapy in accordance with the dosing tables below. Drug therapy, administration and duration is dependent on the treatment arm (Intensive A, Intensive B, Intensive C) the participant is randomised to. Drug dosing is based on the participants age (<18 or ≥18 years of age). The start and end points of each drug therapy, the dose of each drug therapy used, any changes in dosing and all concomitant medications used will be required to be entered into the CRF.

There are currently three proposed treatment arms in the intensive therapy phase. Randomisation – Short Intensive dictates the drug therapy that participants will be randomised to. Treatment Arm A is the reference arm (i.e., control).

Intensive Arm A	**Intensive Arm B**	**Intensive Arm C**
1. IV amikacin, and; 2. IV tigecycline, and; 3. IV imipenem/cilastatin or IV cefoxitin, and; 4. Oral azithromycin or oral clarithromycin, and; 5. Oral clofazimine.	1. Inhaled amikacin, and; 2. IV tigecycline, and; 3. IV imipenem/cilastatin or IV cefoxitin, and; 4. Oral azithromycin or oral clarithromycin, and; 5. Oral clofazimine.	1. IV amikacin, and; 2. IV tigecycline, and; 3. IV imipenem/cilastatin or IV cefoxitin, and; 4. Oral azithromycin or oral clarithromycin.

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

The intensive therapy dosing regimen tables outlined below are separated by age (adult, paediatric) and by intensive treatment arm (Arm A, Arm B, Arm C). The recommended doses and frequencies are a guideline and participant dosing must also take into account clinical judgement and relevant prescribing information.

Table 1 Intensive therapy dosing regimen for Intensive Arm A in adults

Intensive Arm A: Adult Dosing [A]		
Drug	**Recommended Dose (per dose)**	**Frequency**
IV amikacin	15mg/kg **OR** 20-25mg/kg	Once daily Thrice weekly
Dosing will be made in accordance with British Thoracic Society (BTS) guidelines (13) and is dependent on the physiology, site and therapeutic drug monitoring (TDM) outcomes of each participant. In overweight participants use the ideal body weight calculator or in cases of extremes of actual body weight where body weight is greater than 20% above ideal use the adjusted body weight calculator available in the MoOP. To determine ideal body weight for amputees, refer to for the table in the MoOP describing the percentage of total weight contributed by individual body parts.		
IV tigecycline	25mg increasing by 5mg every two doses until either 50mg reached or until patient is unable to tolerate.	Twice daily or same total daily dose over a 24-hour infusion
IV imipenem/cilastatin *IV imipenem/cilastatin is preferred but if not tolerated, use IV cefoxitin.*	**≥50kg** 1g (dose based on imipenem component)	Twice – four times daily infused over 1-4 hours as tolerated
	<50kg 15 – 25mg/kg (dose based on imipenem component). Maximum 1g.	Twice – four times daily infused over 1-4 hours as tolerated
IV cefoxitin *Cefoxitin only for use if imipenem/cilastatin not tolerated.*	2 – 4g	Thrice daily infused over 1-4 hours as tolerated, or same total daily dose over a 24-hour infusion.
Oral azithromycin *If azithromycin not tolerated, use oral clarithromycin.*	250 – 500mg **<40kg or poorly tolerated** 250mg	Once daily Once daily
Oral clarithromycin *Clarithromycin only for use if azithromycin not tolerated.*	500mg	Twice daily
Oral clofazimine	100 – 300mg	Once daily
For participants with confirmed mixed NTM (slow growers + MABS) infections, there is an option to add oral ethambutol to the treatment arm in accordance with the dosing below.		
Oral ethambutol Ethambutol should be dosed on ideal body weight.	15mg/kg (rounded to account for tablet strength) **OR** 25mg/kg (rounded to account for tablet strength)	Once daily Thrice weekly

[A] The recommended doses and frequencies are a guideline and participant dosing must also consider clinical judgement and relevant prescribing information.

Table 2 Intensive therapy dosing regimen for Intensive Arm B in adults

Intensive Arm B: Adult Dosing [A]		
Drug	**Recommended Dose (per dose)**	**Frequency**
Inhaled amikacin (IA) **(IV formulation)**	500mg	Twice daily
IV tigecycline	25mg increasing by 5mg every two doses until either 50mg reached or until patient is unable to tolerate.	Twice daily or same total daily dose over a 24-hour infusion
IV imipenem/cilastatin *IV imipenem/cilastatin is preferred but if not tolerated, use IV cefoxitin.*	**≥50kg** 1g (dose based on imipenem component)	Twice – four times daily infused over 1-4 hours as tolerated
	<50kg 15 – 25mg/kg (dose based on imipenem component). Maximum 1g.	Twice – four times daily infused over 1-4 hours as tolerated
IV cefoxitin *Cefoxitin only for use if imipenem/cilastatin not tolerated.*	2 – 4g	Thrice daily infused over 1-4 hours as tolerated, or same total daily dose over a 24-hour infusion.
Oral azithromycin	250 – 500mg	Once daily
If azithromycin not tolerated, use oral clarithromycin.	**<40kg or poorly tolerated** 250mg	Once daily
Oral clarithromycin *Clarithromycin only for use if azithromycin not tolerated.*	500mg	Twice daily
Oral clofazimine	100 – 300mg	Once daily
For participants with confirmed mixed NTM (slow growers + MABS) infections, there is an option to add oral ethambutol to the treatment arm in accordance with the dosing below.		
Oral ethambutol Ethambutol should be dosed on ideal body weight.	15mg/kg (round to account for tablet strength) **OR** 25mg/kg (round to account for tablet strength)	Once daily Thrice weekly

[A] The recommended doses and frequencies are a guideline and participant dosing must also consider clinical judgement and relevant prescribing information.

Table 3 Intensive therapy dosing regimen for Intensive Arm C in adults

Intensive Arm C: Adult Dosing [A]		
Drug	**Recommended Dose (per dose)**	**Frequency**
IV amikacin	15 mg/kg **OR** 20-25mg/kg	Once daily Thrice weekly
Dosing will be made in accordance with British Thoracic Society (BTS) guidelines (13) and is dependent on the physiology, site and therapeutic drug monitoring (TDM) outcomes of each participant. In overweight participants use the ideal body weight calculator or in cases of extremes of actual body weight where body weight is greater than 20% above ideal use the adjusted body weight calculator available in the MoOP. To determine ideal body weight for amputees, refer to for the table in the MoOP describing the percentage of total weight contributed by individual body parts.		
IV tigecycline	25mg increasing by 5mg every two doses until either 50mg reached or until patient is unable to tolerate.	Twice daily or same total daily dose over a 24-hour infusion
IV imipenem/cilastatin *IV imipenem/cilastatin is preferred but if not tolerated, use IV cefoxitin.*	**≥50kg** 1g (dose based on imipenem component) **<50kg** 15 – 25mg/kg (dose based on imipenem component). Maximum 1g.	Twice – four times daily infused over 1-4 hours as tolerated Twice – four times daily infused over 1-4 hours as tolerated
IV cefoxitin *Cefoxitin only for use if imipenem/cilastatin not tolerated.*	2 – 4g	Thrice daily infused over 1-4 hours as tolerated, or same total daily dose over a 24-hour infusion.
Oral azithromycin *If azithromycin not tolerated, use oral clarithromycin.*	250 – 500mg **<40kg or poorly tolerated** 250mg	Once daily Once daily
Oral clarithromycin *Clarithromycin only for use if azithromycin not tolerated.*	500mg	Twice daily
For participants with confirmed mixed NTM (slow growers + MABS) infections, there is an option to add oral ethambutol to the treatment arm in accordance with the dosing below.		
Oral ethambutol Ethambutol should be dosed on ideal body weight.	15mg/kg (round to account for tablet strength) **OR** 25mg/kg (round to account for tablet strength)	Once daily Thrice weekly

[A] The recommended doses and frequencies are a guideline and participant dosing must also consider clinical judgement and relevant prescribing information.

Table 4 Intensive therapy dosing regimen for Intensive Arm A in paediatrics

Intensive Arm A: Paediatric Dosing [A]			
Drug		**Recommended Dose (per dose)**	**Frequency**
IV amikacin		15-30mg/kg, max 1500mg initial dose	Once daily
Dosing will be made in accordance with BTS guidelines (13) and is dependent on the physiology, site and TDM outcomes of each participant. In obese participants, use the ideal body weight calculator or in cases of extremes of actual body weight where body weight is greater than 20% above ideal body weight use the adjusted body weight calculator available in the MoOP. To determine ideal body weight or adjusted body weight for amputees, refer to for the table in the MoOP describing the percentage of total weight contributed by individual body parts.			
IV tigecycline (ages ≥8 years)	Day 1: (50% of optimal dose)	0.6mg/kg, max 25mg	Twice daily (12 hourly)
	Day 2: (75% of optimal dose)	0.6mg/kg, max 25mg	In the morning
		1.2mg/kg, max 50mg	At night
	Day 3: (100% of optimal dose)	1.2mg/kg, max 50mg	Twice daily (12 hourly)
IV imipenem/cilastatin *IV imipenem/cilastatin is preferred but if not tolerated, use IV cefoxitin.*	Day 1-2	15 - 25mg/kg, max 1g (dose based on imipenem component)	Twice daily (12 hourly)
	Day 3	15 - 25mg/kg, max 1g (dose based on imipenem component)	Four times daily (reduce to 3 times daily if not tolerated) (6 or 8 hourly)
IV cefoxitin *Only for use if imipenem/cilastatin not tolerated.*		40mg/kg, max 2g	Four times daily (6 hourly)
Oral azithromycin *If azithromycin not tolerated, use oral clarithromycin.*		10mg/kg, max 500mg	Once daily
Oral clarithromycin *Only for use if azithromycin not tolerated.*	**Children 1 month – 11 years of age**		
	<8 kg	7.5mg/kg	Twice daily
	8-11 kg	62.5mg	
	12-19 kg	125mg	
	20-29 kg	187.5mg	
	30-40 kg	250mg	
	Children 12-18 years of age		
	Dosing independent of weight	500mg	Twice daily
Oral clofazimine Dosing may be rounded to account for capsule strength.		**<40kg** 3-5mg/kg, max 100mg	Once daily
		≥40kg 100mg	
For participants with confirmed mixed NTM (slow growers + MABS) infections, there is an option to add oral ethambutol to the treatment arm in accordance with the dosing below.			
Oral ethambutol Ethambutol should be dosed on ideal body weight.		15mg/kg, max 1200mg (round to account for tablet strength)	Once daily

[A] The recommended doses and frequencies are a guideline and participant dosing must also consider clinical judgement and relevant prescribing information.

Table 5 Intensive therapy dosing regimen for Intensive Arm B in paediatrics

Intensive Arm B: Paediatric Dosing [A]			
Drug		**Recommended Dose (per dose)**	**Frequency**
Inhaled amikacin (IA) (IV formulation)		500mg	Twice daily
IV tigecycline (ages ≥8 years)	Day 1: (50% of optimal dose)	0.6mg/kg, max 25mg	Twice daily (12 hourly)
	Day 2: (75% of optimal dose)	0.6mg/kg, max 25mg	In the morning
		1.2mg/kg, max 50mg	At night
	Day 3: (100% of optimal dose)	1.2mg/kg, max 50mg	Twice daily (12 hourly)
IV imipenem/cilastatin *IV imipenem/cilastatin is preferred but if not tolerated, use IV cefoxitin.*	Day 1-2	15 - 25mg/kg, max 1g. (dose based on imipenem component)	Twice daily (12 hourly)
	Day 3	15 - 25mg/kg, max 1g (dose based on imipenem component)	Four times daily (reduce to 3 times daily if not tolerated) (6 or 8 hourly)
IV cefoxitin *Only for use if imipenem/cilastatin not tolerated.*		40mg/kg, max 2g	Four times daily (6 hourly)
Oral azithromycin *If azithromycin not tolerated, use oral clarithromycin.*		10mg/kg, max 500mg	Once daily
Oral clarithromycin *Only for use if azithromycin not tolerated.*	**Children 1 month – 11 years of age**		
	<8 kg	7.5mg/kg	Twice daily
	8-11 kg	62.5mg	
	12-19 kg	125mg	
	20-29 kg	187.5mg	
	30-40 kg	250mg	
	Children 12-18 years of age		
	Dosing independent of weight	500mg	Twice daily
Oral clofazimine Dosing may be rounded to account for capsules strength.		**<40kg** 3-5mg/kg, max 100mg	Once daily
		≥40kg 100mg	
For participants with confirmed mixed NTM (slow growers + MABS) infections, there is an option to add oral ethambutol to the treatment arm in accordance with the dosing below.			
Oral ethambutol Ethambutol should be dosed on ideal body weight.		15mg/kg, max 1200mg (round to account for tablet strength)	Once daily

[A] The recommended doses and frequencies are a guideline and participant dosing must also consider clinical judgement and relevant prescribing information.

Table 6 Intensive therapy dosing regimen for Intensive Arm C in paediatrics

Intensive Arm C: Paediatric Dosing [A]			
Drug		**Recommended Dose (per dose)**	**Frequency**
IV amikacin		15-30mg/kg, max 1500mg initial dose	Once daily
Dosing will be made in accordance with BTS guidelines (13) and is dependent on the physiology, site and TDM outcomes of each participant. In obese participants, use the ideal body weight calculator or in cases of extremes of actual body weight where body weight is greater than 20% above ideal body weight use the adjusted body weight calculator available in the MoOP. To determine ideal body weight or adjusted body weight for amputees, refer to for the table in the MoOP describing the percentage of total weight contributed by individual body parts.			
IV tigecycline (ages ≥8 years)	Day 1: (50% of optimal dose)	0.6mg/kg, max 25mg	Twice daily (12 hourly)
	Day 2: (75% of optimal dose)	0.6mg/kg, max 25mg	In the morning
		1.2mg/kg, max 50mg	At night
	Day 3: (100% of optimal dose)	1.2mg/kg, max 50mg	Twice daily (12 hourly)
IV imipenem/cilastatin *IV imipenem/cilastatin is preferred but if not tolerated, use IV cefoxitin.*	Day 1-2	15 - 25mg/kg, max 1g. (dose based on imipenem component)	Twice daily (12 hourly)
	Day 3	15 - 25mg/kg, max 1g (dose based on imipenem component)	Four times daily (reduce to 3 times daily if not tolerated) (6 or 8 hourly)
IV cefoxitin *Only for use if imipenem/cilastatin not tolerated.*		40mg/kg, max 2g	Four times daily (6 hourly)
Oral azithromycin *If azithromycin not tolerated, use oral clarithromycin.*		10mg/kg, max 500mg	Once daily
Oral clarithromycin *Only for use if azithromycin not tolerated.*	**Children 1 month – 11 years of age**		
	<8 kg	7.5mg/kg	Twice daily
	8-11 kg	62.5mg	
	12-19 kg	125mg	
	20-29 kg	187.5mg	
	30-40 kg	250mg	
	Children 12-18 years of age		
	Dosing independent of weight	500mg	Twice daily
For participants with confirmed mixed NTM (slow growers + MABS) infections, there is an option to add oral ethambutol to the treatment arm in accordance with the dosing below.			
Oral ethambutol Ethambutol should be dosed on ideal body weight.		15mg/kg, max 1200mg (round to account for tablet strength)	Once daily

[A] The recommended doses and frequencies are a guideline and participant dosing must also consider clinical judgement and relevant prescribing information.

9.3.1 DRUG SUPPLY, STORAGE AND DISTRIBUTION DURING INTENSIVE THERAPY

Supply, distribution and storage of drugs will be the responsibility of the site coming from site/institution pharmacy stocks as per standard of care and in accordance with site specific guidelines and requirements.

9.3.2 OPTIONS FOR REDUCING NAUSEA DURING INTENSIVE THERAPY

Titration of dosing for imipenem and tigecycline is described in tables 1 to 6. Imipenem should also be given over 2-3 hours (where possible) to reduce nausea. Suggested pharmacological treatment options that could be considered to manage nausea are provided in the FOR*Ma*T Trial Site MoOP.

10 NESTED STUDY A1.3: CONSOLIDATION THERAPY

10.1 INTRODUCTION

Currently, the guidelines for consolidation therapy (13) suggest that patients with isolates that are sensitive to macrolides or that have inducible resistance should be managed with a combination of between one and three oral antibiotics based on drug susceptibility of the isolate and tolerance in combination with IA. Those with isolates that have constitutive resistance should use a combination of between two and four oral drugs based on susceptibility and tolerance in combination with IA. In addition, guidelines suggest that patients with isolates that have amikacin resistance could substitute IA for an alternative oral antibiotic. It is suggested that treatment should continue for 12 months after culture conversion.

There is currently no evidence for any of these guidelines. IA is costly and requires time and effort for maintenance of hygienic practice and drug delivery. Furthermore, adherence to inhaled therapies over the longer term is variable (17-19). This study will examine the effects of IA in addition to the oral only thus providing some evidence regarding the use of additional IA during consolidation. The timing of consolidation therapy is only 46 weeks for this trial. Microbiological clearance will be determined from culture of respiratory samples (sputum (expectorated or induced)) collected ***at least one week apart*** or BAL as follows:

Participants who continue to produce sputum samples during the consolidation phase are requested to provide additional sputum samples monthly. Three consecutive sputum samples will be collected at least one week apart over the last 6 weeks of consolidation therapy. A final sputum sample collected four weeks after cessation of consolidation therapy will together determine the final outcome of microbiological clearance. All four samples will need to be clear to determine clearance.

For participants who continue to have positive sputum cultures at the end of consolidation, a gap in therapy to complete final outcomes may not be required if ongoing treatment is clinically required as microbiological clearance will not have occurred.

Participants must cease treatment for 4 weeks at the end of consolidation prior to the final outcome measures to enable assessment of microbiological clearance without antibiotic suppression.
For participants who are unproductive of sputum and/or induced sputum during the consolidation phase, or who become unproductive of sputum and/or induced sputum during the course of consolidation therapy, a BAL is to be performed at final outcome (4 weeks after completing consolidation therapy).

10.2 OBJECTIVES

10.2.1 PRIMARY OBJECTIVE

To compare the microbiological clearance with good tolerability of MABS between those allocated to consolidation therapy with oral treatment and those allocated to consolidation therapy with oral treatment and additional IA at Final Outcome.

10.2.2 SECONDARY OBJECTIVES

1. To compare microbiological clearance (irrespective of toxicity) at Final Outcome between those allocated to consolidation therapy with oral treatment and those allocated to consolidation therapy with oral treatment and additional IA taking into account microbiological status at the start of consolidation.
2. Difference in safety between those allocated to consolidation therapy with oral treatment and those allocated to consolidation therapy with oral therapy and additional IA.
3. Change in FEV1 z-score between start of consolidation therapy and Final Outcome between those allocated to consolidation therapy with oral treatment and those allocated to consolidation therapy with oral therapy and additional IA taking into account microbiological clearance at Final Outcome.
4. Change in 6MWD between Week 12 of the trial and Final Outcome between adult participants allocated to consolidation therapy with oral treatment and those allocated to consolidation therapy with oral therapy and additional IA taking into account microbiological clearance at Final Outcome.
5. Change in CT scan parameters (bronchiectasis, mucus plugging, airway wall thickening, atelectasis, % disease and air trapping), between 12 weeks and Final Outcome taking into account microbiological clearance at start of consolidation therapy between those allocated to consolidation therapy with oral treatment and those allocated to consolidation therapy with oral therapy and additional IA.
6. Changes in HRQoL (CFQ-R) for participants with CF between start of consolidation therapy and Final Outcome between those allocated to consolidation therapy with oral treatment and those allocated to consolidation therapy with oral therapy and additional IA.
7. To examine general HRQoL between start of consolidation therapy and Final Outcome in adults (CF and non-CF) between those allocated to consolidation therapy with oral treatment and those allocated to consolidation therapy with oral therapy and additional IA.
8. To compare the cost effectiveness of consolidation between those allocated to consolidation therapy with oral treatment and those allocated to consolidation therapy with oral therapy and additional IA.
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 those allocated to consolidation therapy with oral treatment and those allocated to consolidation therapy with oral therapy and additional IA.

10.3 ELIGIBILITY CRITERIA

Participants who have been randomised to intensive therapy in Appendix A1 and have either completed intensive therapy or who are unable to complete Intensive therapy due to a lack of tolerance.

.

10.4 STATISTICAL ANALYSIS

Details of the sample size calculation for this study are presented in Section 6.0 of the Master Protocol and the relevant section of Appendix F: General Statistical Principles and in the SAP.

10.5 CONSOLIDATION THERAPY DOSING REGIMEN

Following R-Con, participants will receive consolidation treatment in accordance with the dosing tables below. Drug therapy, administration and duration is dependent on the treatment arm (Consolidation Arm a and Consolidation Arm b), age, and/or weight of the participant. The start and end points of each drug therapy, the dose of each drug therapy used, any changes in dosing, and all concomitant medications used will be required to be entered into the CRF.

There are currently two proposed treatment arms that participants will be randomised to during consolidation therapy.

Consolidation Arm a	**Consolidation Arm b**
1. Oral clofazimine, and; 2. Oral azithromycin or oral clarithromycin, and; In combination with one to three of the following oral antibiotics: • Oral linezolid, • Oral trimethoprim / sulfamethoxazole, • Oral bedaquiline, • Oral rifabutin, • Oral doxycycline, • Oral moxifloxacin.	1. Inhaled amikacin 2. Oral clofazimine, and; 3. Oral azithromycin or oral clarithromycin, and; In combination with one to three of the following oral antibiotics: • Oral linezolid, • Oral trimethoprim / sulfamethoxazole, • Oral bedaquiline, • Oral rifabutin, • Oral doxycycline, • Oral moxifloxacin.

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

The consolidation therapy dosing regimen tables outlined below are separated by age (adult, paediatric) and by consolidation treatment arm (Arm a and Arm b). The recommended doses and frequencies are a guideline and participant dosing must also take into account clinical judgement and relevant prescribing information.

Table 7 Consolidation therapy dosing regimen for Consolidation Arm a in adults

Consolidation Arm a: Adult Dosing[A]		
Drug	**Recommended Dose (per dose)**	**Frequency**
Oral clofazimine	100 – 300mg	Once daily
Oral azithromycin	250 – 500mg **OR** 500mg	Once daily Thrice weekly
If azithromycin not tolerated, use oral clarithromycin.	**<40kg or poorly tolerated** 250mg	 Thrice weekly
Oral clarithromycin *Clarithromycin only for use if azithromycin not tolerated.*	500mg	Twice daily
In combination with one to three of the following oral antibiotics guided by participant susceptibility and tolerance.		
Oral linezolid	600mg	Once daily
Oral trimethoprim with sulfamethoxazole	160mg/800mg	Twice daily
Oral bedaquiline *(Weighing at least 30kg)*	**First 2 weeks** 400mg	Once daily
	For remaining 22 weeks 200mg Max duration 6 months	Thrice weekly At least 48 hours between doses
Oral rifabutin	5mg/kg, max 450mg	Once daily
Oral doxycycline	100mg	Once daily
Oral moxifloxacin	400mg	Once daily
For participants with confirmed mixed NTM (slow growers + MABS) infections, there is an option to add oral ethambutol to the treatment arm in accordance with the dosing below.		
Oral ethambutol Ethambutol should be dosed on ideal body weight.	15mg/kg (round to account for tablet strength) **OR** 25mg/kg (round to account for tablet strength)	Once daily Thrice weekly

[A] The recommended doses and frequencies are a guideline and participant dosing must also consider clinical judgement and relevant prescribing information.

Table 8 Consolidation therapy dosing regimen for Consolidation Arm b in adults

Consolidation Arm b: Adult Dosing [A]		
Drug	**Recommended Dose (per dose)**	**Frequency**
Inhaled amikacin (IA) **(IV formulation)**	500mg	Twice daily
Oral clofazimine	100 – 300mg	Once daily
Oral azithromycin	250 – 500mg **OR** 500mg	Once daily Thrice weekly
If azithromycin not tolerated, use oral clarithromycin.	**<40kg or poorly tolerated** 250mg	 Thrice weekly
Oral clarithromycin *Clarithromycin only for use if azithromycin not tolerated.*	500mg	Twice daily
In combination with one to three of the following oral antibiotics guided by participant susceptibility and tolerance.		
Oral linezolid	600mg	Once daily
Oral trimethoprim with sulfamethoxazole	160mg/800mg	Twice daily
Oral bedaquiline *(Weighing at least 30kg)*	**First 2 weeks** 400mg	Once daily
	For remaining 22 weeks 200mg Max duration 6 months	Thrice weekly At least 48 hours between doses
Oral rifabutin	5mg/kg, max 450mg	Once daily
Oral doxycycline	100mg	Once daily
Oral moxifloxacin	400mg	Once daily
For participants with confirmed mixed NTM (slow growers + MABS) infections, there is an option to add oral ethambutol to the treatment arm in accordance with the dosing below.		
Oral ethambutol Ethambutol should be dosed on ideal body weight.	15mg/kg (round to account for tablet strength) **OR** 25mg/kg (round to account for tablet strength)	Once daily Thrice weekly

[A] The recommended doses and frequencies are a guideline and participant dosing must also consider clinical judgement and relevant prescribing information.

Table 9 Consolidation therapy dosing regimen for Consolidation Arm a in paediatrics

Consolidation Arm a: Paediatric Dosing [A]			
Drug		**Recommended Dose (per dose)**	**Frequency**
Oral clofazimine Dosing may be rounded to account for capsules.		**<40kg** 3-5mg/kg, max 100mg	Once daily
		≥40kg 100mg	
Oral azithromycin *If azithromycin not tolerated, use oral clarithromycin.*		10mg/kg, max 500mg	Once daily
Oral clarithromycin *Only for use if azithromycin not tolerated.*	**Children 1 month – 11 years of age**		
	<8 kg	7.5mg/kg	Twice daily
	8-11 kg	62.5mg	
	12-19 kg	125mg	
	20-29 kg	187.5mg	
	30-40 kg	250mg	
	Children 12-18 years of age		
	Dosing independent of weight	500mg	Twice daily
In combination with one to three of the following oral antibiotics guided by participant susceptibility and tolerance.			
Oral linezolid	1 month – 9 years	10mg/kg, max 450mg	Twice daily
	10 – 12 years	10mg/kg, max 600mg	Daily
	>12 years	600mg	Daily
Oral trimethoprim with sulfamethoxazole		5mg/kg trimethoprim max 160mg trimethoprim	Twice daily
Oral bedaquiline **(age ≥5 years)**	**Weeks 1 and 2**		
	≥15kg - <20kg	160mg	Once daily
	≥20kg - <30kg	200mg	
	≥30kg	400mg	
	Weeks 3-24 - Max Duration 6 Months		
	≥15kg - <20kg	80mg	Thrice weekly. At least 48 hours between doses
	≥20kg - <30kg	100mg	
	≥30kg	200mg	
Oral rifabutin		5mg/kg, max 300mg	Once daily
Oral doxycycline **(ages ≥8 years)**		2mg/kg, max 100mg	Once daily
Oral moxifloxacin Dosing may be rounded to account for capsules.		10-15mg/kg, max 400mg	Once daily
For participants with confirmed mixed NTM (slow growers + MABS) infections, there is an option to add oral ethambutol to the treatment arm in accordance with the dosing below.			
Oral ethambutol Ethambutol should be dosed on ideal body weight.		15mg/kg, max 1200mg (round to account for tablet strength)	Once daily

[A] The recommended doses and frequencies are a guideline and participant dosing must also consider clinical judgement and relevant prescribing information.

Table 10 Consolidation therapy dosing regimen for Consolidation Arm b in paediatrics

Consolidation Arm b: Paediatric Dosing [A]			
Drug		**Recommended Dose (per dose)**	**Frequency**
Inhaled amikacin (IA) (IV formulation)		500mg	Twice daily
Oral clofazimine Dosing may be rounded to account for capsules.		**<40kg** 3-5mg/kg, max 100mg	Once daily
		≥40kg 100mg	
Oral azithromycin *If azithromycin not tolerated, use oral clarithromycin.*		10mg/kg, max 500mg	Once daily
Oral clarithromycin *Only for use if azithromycin not tolerated.*	**Children 1 month – 11 years of age**		
	<8 kg	7.5mg/kg	Twice daily
	8-11 kg	62.5mg	
	12-19 kg	125mg	
	20-29 kg	187.5mg	
	30-40 kg	250mg	
	Children 12-18 years of age		
	Dosing independent of weight	500mg	Twice daily
In combination with one to three of the following oral antibiotics guided by participant susceptibility and tolerance.			
Oral linezolid	1 month – 9 years	10mg/kg, max 450mg	Twice daily
	10 – 12 years	10mg/kg, max 600mg	Daily
	>12 years	600mg	Daily
Oral trimethoprim with sulfamethoxazole		5mg/kg trimethoprim max 160mg trimethoprim	Twice daily
Oral bedaquiline (age ≥5 years)	**Weeks 1 and 2**		
	≥15kg - <20kg	160mg	Once daily
	≥20kg - <30kg	200mg	
	≥30kg	400mg	
	Weeks 3-24 - Max Duration 6 Months		
	≥15kg - <20kg	80mg	Thrice weekly. At least 48 hours between doses
	≥20kg - <30kg	100mg	
	≥30kg	200mg	
Oral rifabutin		5mg/kg, max 300mg	Once daily
Oral doxycycline (ages ≥8 years)		2mg/kg, max 100mg	Once daily
Oral moxifloxacin Dosing may be rounded to account for capsules.		10-15mg/kg, max 400mg	Once daily
For participants with confirmed mixed NTM (slow growers + MABS) infections, there is an option to add oral ethambutol to the treatment arm in accordance with the dosing below.			
Oral ethambutol Ethambutol should be dosed on ideal body weight.		15mg/kg, max 1200mg (round to account for tablet strength)	Once daily

[A] The recommended doses and frequencies are a guideline and participant dosing must also consider clinical judgement and relevant prescribing information.

10.5.1 DRUG SUPPLY, STORAGE AND DISTRIBUTION DURING CONSOLIDATION THERAPY

Supply, distribution and storage of drugs will be the responsibility of the site coming from site/institution pharmacy stocks as per standard of care and made in accordance with site-specific guidelines and requirements.

10.5.2 DRUG COMPLIANCE DURING CONSOLIDATION THERAPY

The procedures for distribution of consolidation therapy are site dependent. Drug compliance during consolidation therapy will be captured from pharmacy records of drugs dispensed to the participant while enrolled in FOR*Ma*T Appendix A1.

11 SCHEDULE OF ASSESSMENTS

Table 11 lists the special considerations that are applicable to all Schedule of Assessment tables. Table 11 must be used in conjunction with Tables 12 to 14. Tables 12 to 14 show the schedules of assessment tables for participants enrolled in Appendix A1. Table 12 shows the schedule of assessments for all participants from Screening to end of Week 6, Table 13 shows the schedule of assessments from Week 7 to Week 12 for participants randomised to Prolonged Intensive and Table 14 shows the schedule of assessments for all participants during the Consolidation therapy phase and at the Final Outcome. Acceptable stud[08yy visit windows are also outlined in tables 12 to 14.

Table 11 Special considerations for Schedule of Assessments

Symbol	Definition
A	Participant reconsent is required with IRB/ IED/HREC approved changes to the protocol that affect the participants rights and/or safety and/or if a child turns 18 years old during the trial and must reconsent as an adult participant.
B	Visits may be conducted while an inpatient or at home if participant is receiving home-based care.
C	To be eligible to enrol in the Intervention Program, the participant is required to have either two (2) MABS-positive sputum samples or one (1) MABS-positive BAL sample. Refer to section 7.3 for further information.
D	To determine MABS clearance following four (4) weeks of intensive therapy, three sputum samples or one BAL sample are required to be collected in Week 4 (±3 days) to ensure results are available by week 6 of intensive therapy to inform randomisation.
E	Adult height is to be recorded once (preferably at the screening visit). Paediatric height must be measured at least every six weeks.
F	Only required if the screening assessments were reviewed more than two (2) weeks earlier than Day 1.
G	Refer to section 7.2 for eligibility criteria for the screening visit chest CT.
H	Only required in female participants of childbearing potential. A serum pregnancy test is required at screening and final study visit. A urine or serum pregnancy test is acceptable at all other times.
I	Screening audiology and screening vestibular assessment can be performed if a participant has commenced intensive therapy but must be performed within three (3) days of first receiving treatment.
J	QT interval at screening is to be corrected using the Fridericia method. Any subsequent abnormal QTc intervals are to be confirmed using the Fridericia method.
K	Six-minute walk test to be performed in participants ≥18 years of age only.
L	Plasma levels post inhaled amikacin are to be collected 90 minutes post dose (range 60 to 120 minutes). Please record inhaled amikacin start and stop times.
M	IV Amikacin Therapeutic Drug Monitoring to be completed within 48 hours of dosing according to site protocol.
N	The EQ-5D-5L is to be administered to participants ≥18 years of age whereas the EQ-5D-Y is to be administered to participants 8 to 17 years of age. The EQ-5D-Y Proxy is to be administered to parents/carers of participants 4 to 7 years of age.
O	The SF-36 is to be administered to participants ≥16 years of age at time of Screening. For participants aged <16 years at Screening, the PedsQL™ is to be used for entire duration of trial.
P	The PedsQL™ is only to be assessed in participants <16 years of age at time of Screening. If both the PedsQL™ and the CFQ-R are administered where possible, the PedsQL™ should be administered prior to the CFQ-R.
Q	The CFQ-R is only to be completed in participants with CF. The age appropriate CFQ-R assessment should be selected; CFQ-R adult/teen (≥14 years of age), CFQ-R child (6 to 13 years of age) and CFQ-R parent (parent/carer of participant 6 to 13 years of age).
R	The Child Health Utility is only to be assessed in participants 7 to 17 years of age.

S	The SGRQ is only to be assessed in non-CF participants 18 years of age and older.
T	Costs questionnaire only required for participants that are randomised to immediate consolidation.
U	MARS-5 is only to be completed in participants in the intervention cohort on outpatient based MABS-PD treatment.
V	Week 12 chest CT scan is optional and requires participant to consent to FOR*Ma*T Sub-Study C3: Imaging. The site must have approval to conduct this additional scan, be certified to perform the scan using the scanner specific protocol and the participant must provide additional consent.
W	To determine MABS clearance following ten (10) weeks of intensive therapy, three sputum samples or one BAL sample are required to be collected in Week 10 (±3 days).
X	Participants unable to produce a sputum sample (expectorated or induced) to be marked as unproductive on the CRF.
Y	Participants who have produced sputum samples during Weeks 18, 28, and 38 are requested to provide three additional sputum samples collected at least one week apart nearer to the end of Weeks 52. For participants who were unproductive (intermittent or continual) during Weeks 18, 28, 38 and 52, a BAL sample is to be collected during Week 56.
Z	Clinic visit and some assessments at Week 10 can be completed at any time between Week 10 and Week 12.
1	Chest CT scan at early withdrawal visit will only be requested if clinically indicated.

Table 12 Schedule of Assessments for Intervention Program Participants: Intensive Therapy (Screening and first six weeks of intensive therapy)

ASSESSMENT		SCREENING VISIT	INTENSIVE THERAPY Week 1 - Week 6						
		Day 0 ***-42 Days***	**Day 1** ***+24 hours***	**Week 1** ***+3 Days***	**Week 2** ***±3 Days***	**Week 3** ***±3 Days***	**Week 4** ***±3 Days***	**Week 5** ***±3 Days***	**Week 6** ***±3 Days***
Informed consent for Appendix A1[A]		✓							
Clinic visit [B]		✓	✓	✓	✓	✓	✓	✓	✓
Review eligibility		✓							
Randomisation			✓						✓
Adverse event monitoring			✓	✓	✓	✓	✓	✓	✓
Respiratory sample	Sputum (expectorated or induced) ***or;***	✓[C]					✓ x3[D]		
	BAL	✓[C]					✓[D]		
Height [E] and Weight		✓							✓
Medication Review		✓	✓[F]	✓	✓	✓	✓	✓	✓
Spirometry		✓							✓
Chest CT		✓[G]							
Pregnancy Test and Breastfeeding Status [H]		✓	✓		✓		✓		✓
Audiogram		✓[I]					✓		
Vestibular Monitoring		✓[I]					✓		
ECG [J]		✓			✓				✓
6-minute walk test [K]		✓							
Blood collection:									
1. Chemistry and Renal Function		✓		✓	✓	✓	✓	✓	✓
2. Liver Function Tests		✓		✓	✓	✓	✓	✓	✓
3. Full Blood Count		✓		✓	✓	✓	✓	✓	✓
Physical examination		✓	✓[F]						✓
Amikacin monitoring	Therapeutic Drug Monitoring, ***or;***		✓[M] Arm A & C		✓ Arm A & C				✓ Arm A & C
	Post dose levels [L]			✓ Arm B only					
Health-related quality of life questionnaires:									
1. EQ-5D-5L or -Y [N]		✓							✓
2. SF36 [O]		✓							✓
3. PedsQL™ [P]		✓							✓
4. CFQ-R [Q]		✓							✓

ASSESSMENT	SCREENING VISIT	INTENSIVE THERAPY Week 1 - Week 6						
	Day 0 ***-42 Days***	**Day 1** ***+24 hours***	**Week 1** ***+3 Days***	**Week 2** ***±3 Days***	**Week 3** ***±3 Days***	**Week 4** ***±3 Days***	**Week 5** ***±3 Days***	**Week 6** ***±3 Days***
5. Child Health Utility 9D [R]	✓							✓
6. SGRQ [S]	✓							✓
Costs Questionnaire	✓							✓
Medication Adherence Questionnaire [U]								✓

Table 13 Schedule of Assessments for Intervention Program Participants: Prolonged Intensive Therapy(Total of 12 weeks of intensive therapy)

ASSESSMENT		PROLONGED INTENSIVE THERAPY Week 7- Week 12					
		Week 7 ***±3 Days***	**Week 8** ***±3 Days***	**Week 9** ***±3 Days***	**Week 10** ***±3 Days***	**Week 11** ***±3 Days***	**Week 12** ***±3 Days***
Clinic visit [B]		✓	✓	✓	✓	✓	✓
Randomisation							✓
Adverse event monitoring		✓	✓	✓	✓	✓	✓
Respiratory sample	Sputum (expectorated or induced) ***or;***				✓ x3[W]		
	BAL				✓[W]		
Height [E] and Weight							✓
Medication Review		✓	✓	✓	✓	✓	✓
Spirometry							✓
Chest CT							Optional [V]
Pregnancy Test and Breastfeeding Status [H]				✓			✓
Audiogram			✓				✓
Vestibular Monitoring			✓				✓
ECG[J]							✓
6-minute walk test [K]							✓
Blood collection:							
7. Chemistry and Renal Function		✓	✓	✓	✓	✓	✓
8. Liver Function Tests		✓	✓	✓	✓	✓	✓
9. Full Blood Count		✓	✓	✓	✓	✓	✓
Physical examination							✓
Amikacin Therapeutic Drug Monitoring							✓ Arm A & C
Health-related quality of life questionnaires:							
10. EQ-5D-5L or -Y [N]							✓
11. SF36 [O]							✓
12. PedsQL™ [P]							✓

ASSESSMENT	PROLONGED INTENSIVE THERAPY Week 7- Week 12					
	Week 7 ***±3 Days***	**Week 8** ***±3 Days***	**Week 9** ***±3 Days***	**Week 10** ***±3 Days***	**Week 11** ***±3 Days***	**Week 12** ***±3 Days***
13. CFQ-R [Q]						✓
14. Child Health Utility 9D [R]						✓
15. SGRQ [S]						✓
Costs Questionnaire						✓
Medication Adherence Questionnaire [U]						✓

Table 14 Schedule of Assessments for Consolidation Therapy and Final Outcome

ASSESSMENT	CONSOLIDATION THERAPY										FINAL STUDY VISIT	Early Withdrawal Visit
	Immediate consolidation *After completing six weeks (short) intensive therapy*						Delayed consolidation *After completing 12 weeks (prolonged) intensive therapy*					
	Week 10 *±3 days*	**Week 12** *±3 days*	**Week 18** *±30 days*	**Week 28** *±30 days*	**Week 38** *±30 days*	**End of consolidation (Week 52)** *+5 days*	**Week 18** *±30 days*	**Week 28** *±30 days*	**Week 38** *±30 days*	**End of consolidation (Week 58)** *+5 days*	**+4 weeks post End of consolidation** *+14 days*	**+30 days**
Clinic visit [B]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse event monitoring	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Respiratory sample — Sputum (expectorated or induced) ***or;***	✓ x3[W]		✓[X]	✓[X]	✓[X]	✓[X]	✓[X]	✓[X]	✓[X]	✓[X]	✓[Y]	✓
Respiratory sample — Broncho-alveolar lavage (BAL)	✓[W]											
Height [E] and Weight	✓[Z]	✓		✓		✓		✓		✓	✓	✓
Medication Review	✓[Z]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Spirometry		✓									✓	✓
Chest CT		Optional [V]									✓	✓[1]
Pregnancy Test and Breastfeeding Status [H]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Audiogram		✓		✓				✓			✓	✓
Vestibular Monitoring		✓		✓				✓			✓	✓
ECG [J]		✓		✓				✓			✓	✓
6-minute walk test [K]		✓									✓	✓
Blood collections:												
1. Chemistry and Renal Function	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2. Liver Function Tests	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3. Full Blood Count	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical examination		✓									✓	✓
Health-related quality of life questionnaires:												
4. EQ-5D-5L or -Y [N]		✓									✓	✓
5. SF-36 [O]		✓									✓	✓
6. PedsQL™ [P]		✓									✓	✓
7. CFQ-R [Q]		✓									✓	✓
8. Child Health Utility 9D [R]		✓									✓	✓
9. SGRQ [S]		✓									✓	✓
Costs Questionnaire		✓		✓				✓			✓	✓
Medication Adherence Questionnaire [U]		✓		✓		✓		✓		✓		

12 RANDOMISATION

There will be three stages of randomisation in the Intervention Program Appendix A, dictating the treatment the participant will receive:

***Randomisation to Short Intensive (R-SI)*:** The first randomisation will be at the start of the intensive phase, with all participants randomised between the different intensive therapy arms according to the study specific Appendix.

Randomisation to Prolonged Intensive or Immediate Consolidation (R-PI/IC): The second randomisation will ONLY be 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 short intensive therapy and will allocate participants to either;

> Continue intensive therapy which will be followed by consolidation (participants remain on the same intensive therapy drug regimen if randomised to prolonged intensive therapy),
>
> or immediately commence consolidation therapy.

Randomisation to Consolidation (R-Con): This randomisation will allocate participants to the consolidation therapy arms. Each randomisation will function as a 'quasi-separate' trial (as described in the relevant sections of Appendix A), as well as being considered in combination (intensive + consolidation). Randomisation at each level will be conducted using the method of minimisation (described in the relevant sections of the Master Protocol and Appendix F: General Statistical Principles). Each randomisation level will be planned to enable flexibility via pre-planned adaptations as described above.

13 APPLICABLE DISCOVERY STUDIES AND REGISTRY LINKAGE FOR APPENDIX A1

Intervention Program participants may be eligible to enrol in the following FOR*Ma*T Sub-Studies and Integrated Studies:

1) Appendix C Discovery
   i. C1: Pharmacokinetics
      i) C1.1 Steady state pharmacokinetics of Amikacin
      ii) C1.2 Microsampling and non-blood matrix validation for amikacin TDM
      iii) C1.3 Pharmacokinetics of MABS-PD therapies
      iv) C1.4 Pharmacokinetics of CFTR modulator therapy in persons with CF on MABS therapy
   ii. C2: Immune factors and biomarkers
      i) C2.1 Macrophage function
      ii) C2.2 Mitochondrial stress
      iii) C2.3 T-cell function
      iv) C2.4 Gene expression
      v) C2.5 Serology
   iii. C3: Imaging
2) Appendix D Registry Linkage
   i. D1: Australian cystic fibrosis data registry
3) Appendix E Health Economics
   i. E1: Cost effectiveness and Resource utilisation

Please see the relevant sections of the applicable appendix for further information, including additional eligibility criteria.

14 REFERENCES

1. Food US, Drug A. Guideline for the study and evaluation of gender differences in the clinical evaluation of drugs; notice. Fed Regist. 1993;58(139):39406-16.
2. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-7.
3. Kwan YH, Weng SD, Loh DHF, Phang JK, Oo LJY, Blalock DV, et al. Measurement Properties of Existing Patient-Reported Outcome Measures on Medication Adherence: Systematic Review. J Med Internet Res. 2020;22(10):e19179.
4. Chan AHY, Horne R, Hankins M, Chisari C. The Medication Adherence Report Scale: A measurement tool for eliciting patients' reports of nonadherence. Br J Clin Pharmacol. 2020;86(7):1281-8.
5. Lam WY, Fresco P. Medication Adherence Measures: An Overview. Biomed Res Int. 2015;2015:217047.
6. Vrijens B, Urquhart J. Methods for measuring, enhancing, and accounting for medication adherence in clinical trials. Clin Pharmacol Ther. 2014;95(6):617-26.
7. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther. 1999;21(6):1074-90; discussion 3.
8. Al-Hassany L, Kloosterboer SM, Dierckx B, Koch BC. Assessing methods of measuring medication adherence in chronically ill children-a narrative review. Patient Prefer Adherence. 2019;13:1175-89.
9. Olivier KN, Griffith DE, Eagle G, McGinnis Ii JP, Micioni L, Liu K, et al. Randomized Trial of Liposomal Amikacin for Inhalation in Nontuberculous Mycobacterial Lung Disease. Am J Respir Crit Care Med. 2016.
10. Prevots DR, Marras TK. Epidemiology of human pulmonary infection with nontuberculous mycobacteria: a review. Clin Chest Med. 2015;36(1):13-34.
11. van Ingen J, Totten SE, Helstrom NK, Heifets LB, Boeree MJ, Daley CL. In Vitro Synergy between Clofazimine and Amikacin in Treatment of Nontuberculous Mycobacterial Disease. Antimicrobial Agents and Chemotherapy. 2012;56(12):6324-7.
12. Shen G-H, Wu B-D, Hu S-T, Lin C-F, Wu K-M, Chen J-H. High efficacy of clofazimine and its synergistic effect with amikacin against rapidly growing mycobacteria. International Journal of Antimicrobial Agents. 2010;35(4):400-4.
13. Haworth CS, Banks J, Capstick T, Fisher AJ, Gorsuch T, Laurenson IF, et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax. 2017;72(Suppl 2).
14. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175(4):367-416.
15. Floto RA, Olivier KN, Saiman L, Daley CL, Herrmann JL, Nick JA, et al. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis: executive summary. Thorax. 2016;71(1):88-90.
16. Novosad SA, Beekmann SE, Polgreen PM, Mackey K, Winthrop KL, Team MaS. Treatment of Mycobacterium abscessus Infection. Emerg Infect Dis. 2016;22(3):511-4.

17. Harrison MJ, McCarthy M, Fleming C, Hickey C, Shortt C, Eustace JA, et al. Inhaled versus nebulised tobramycin: A real world comparison in adult cystic fibrosis (CF). Journal of Cystic Fibrosis. 2014;13(6):692-8.
18. Nasr SZ, Chou W, Villa KF, Chang E, Broder MS. Adherence to dornase alfa treatment among commercially insured patients with cystic fibrosis. Journal of Medical Economics. 2013;16(6):801-8.
19. Bakker EM, Volpi S, Salonini E, van Der Wiel-Kooij EC, Sintnicolaas CJJCM, Hop WCJ, et al. Improved treatment response to dornase alfa in cystic fibrosis patients using controlled inhalation. European Respiratory Journal. 2011;38(6):1328-35.