



Finding the Optimal Regimen for *Mycobacterium abscessus* Treatment

APPENDIX A3 - INTERVENTION PROGRAM

Intensive Treatment Phase – Arm D

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ABBREVIATIONS

AMOX	Amoxycillin
BAL	Bronchoalveolar Lavage
BAR	Bayesian Adaptive Randomisation
Bla _{Mab}	MABS major β -lactamase
BLI	β -lactamase inhibitors
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CHU9D	Child Health Utility 9D
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXM	Cefuroxime
DBOs	diazabicyclooctanes
D,D-c	D,D-carboxypeptidases
Ddts	D,D-transpeptidases
DUR	Durlobactam
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in one second
FORMaT	Finding the Optimal Regimen for <i>Mycobacterium abscessus</i> Treatment
HMW PBPs	high-molecular weight penicillin-binding proteins
HRQoL	Health Related Quality of Life
iDSMB	independent data safety monitoring board
IPM	Imipenem

IRB/IEC/HREC	Independent Research Board/Independent Ethics Committee/Human Research Ethics Committee
IST	Innoviva Specialty Therapeutics
IV	Intravenous
Ldts	L,D-transpeptidases
Ldt _{mab2,4}	L,D-transpeptidases from MABS
LMW PBP	low-molecular weight penicillin-binding protein
MABS	<i>Mycobacterium abscessus</i>
MABS-PD	MABS Pulmonary Disease
MARS-5	5-item Medication Adherence Rating Scale
MIC	Minimum Inhibitory Concentration
NTM	Non-Tuberculous Mycobacteria
PedsQL™	Pediatric Quality of Life Inventory
REDCap	Research Electronic Data Capture
R-Con	Randomisation – Consolidation
R-PI/IC	Randomisation – Prolonged Intensive/Immediate Consolidation
R-SI	Randomisation – Short Intensive
SF-36	Short form-36
SGRQ	St George Respiratory Questionnaire
SOC	Standard of Care
SUL	Sulbactam
SUL-DUR	Sulbactam-Durlobactam
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
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. The modules 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.
- The Discovery studies applicable to the module (if relevant).

A description of cost effectiveness methodology and analysis as appropriate will be detailed in Appendix E: Health Economics.

A general description of statistical analyses and simulations are detailed in Appendix F: General Statistical Principles.

APPENDIX A3 – INTENSIVE TREATMENT PHASE – ARM D

Appendix A3 describes Intensive Treatment Arm D, which will be added to the FORMaT Intervention Programs (Appendix A) following the first interim analysis of the FORMaT trial. **Appendix A3 must be reviewed together with Appendix A1.** Interim analysis will consider discontinuing one of the short intensive arms (either arm B or C) to continue to have 3 intensive treatment arms. Arm A remains as the reference Arm.

After completion of the Intensive Treatment Arm D, participants will continue onto the Consolidation Treatment Phase as outlined in Appendix A1.

Within Appendix A3 there are nested studies which are governed by the trial design and conduct described below.

FORMaT Appendix A3 Summary	
Treatment combinations:	<i>Intensive therapy Arm D:</i>
	Arm D
	Weeks 1 to 4 (and Weeks 7 to 10 if randomised to Prolonged Intensive)
	<ol style="list-style-type: none"> 1. IV sulbactam - durlobactam, and; 2. IV ceftriaxone, and; 3. Oral amoxicillin, and; 4. Oral azithromycin or oral clarithromycin, and; 5. Oral clofazimine.
	Weeks 5 to 6 (and Weeks 8 to 12 if randomised to Prolonged Intensive)
	<ol style="list-style-type: none"> 1. Oral clofazimine, and; 2. Oral azithromycin or clarithromycin, and; 3. In combination with one to three of the following oral antibiotics: <ul style="list-style-type: none"> • Linezolid, • Trimethoprim / sulfamethoxazole (co-trimoxazole), • Bedaquiline, • Rifabutin, • Doxycycline, • Moxifloxacin.
	A mixed Non-Tuberculous Mycobacteria (NTM) infection (slow grower + <i>Mycobacterium abscessus</i> (MABS)) can include the use of ethambutol in either/both the intensive or consolidation phase/s of treatment.
Appendix A3-specific eligibility:	Eligibility criteria as per Master Protocol section 4.1, 4.2 and 4.4 and Appendix A1 section 4.1 and 4.3.
Appendix A3-specific inclusions:	<p>Inclusion criteria as per Master Protocol section 4.2 and Appendix A1 section 4.1</p> <p>AND</p> <p>Male or female participants aged 12 years and older.</p>

FORMaT Appendix A3 Summary		
Appendix A3-specific exclusions:	<p>Exclusion criteria as per Master Protocol section 4.2 and Appendix A1 section 4.2 AND</p> <p>Participants aged between 12 and <18years old with clinically significant renal impairment as indicated by an age-appropriate estimated creatinine clearance.</p> <p>Known hypersensitivity to any of the therapies for which no alternative option(s) have been provided. This includes:</p> <ul style="list-style-type: none"> o Sulbactam/durlobactam o Ceftriaxone, o Amoxicillin, o Macrolide antibiotics, and o Clofazimine. 	
Target recruitment:	80 to 100 participants randomised to Arm D.	
Outcome measures:	Primary, Secondary and exploratory outcomes are as per the Master Protocol Section 4.6 and Appendix A1 Section 2.0.	
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	<p>Intensive Therapy Modules:</p> <p>Nested study A3.1: Type of Short intensive Therapy (Arm D versus all other treatment arms detailed in Appendix A1)</p> <p>Nested study A3.2: 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.</p>	

Intensive Therapy Module Nested Studies		
Nested study A3.1: 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 A3.2: 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* (Time Point Final – Prolonged Intensive) or TPF-WK12 (Time Point Final – Week 12):	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.	

1 INTRODUCTION

Appendix A3 describes Intensive Treatment Arm D, which will be added to the FORMaT Intervention Programs (Appendix A) following the first interim analysis of the FORMaT trial. **Appendix A3 must be reviewed together with Appendix A1.**

Sites may undertake intensive treatment detailed in Appendix A1 only. Alternatively, sites may undertake intensive treatment detailed in Appendix A3 and Appendix A1 depending on access to the Appendix A3 study drugs. All sites will undertake consolidation treatment according to Appendix A1.

Background

There has been increasing interest globally in the role of β lactam/ β lactamase combinations for potential treatment of *Mycobacterium abscessus* (MABS). Evidence for this is currently based on in vitro studies with some case reports of clinical outcomes.

Bla_{Mab} is MABS' major β -lactamase responsible for inactivating several β -lactams and is effectively blocked by avibactam but not clavulanate. Genetic inactivation of Bla_{Mab}, however, has little impact on the potency of imipenem (IPM) or ceftiofex. The addition of β lactamase inhibitors (BLIs) such as relebactam to imipenem has only resulted in a 1 to 2 fold change in imipenem MIC distribution so relying on BLIs is unlikely to deliver a drastic potency increase for imipenem and ceftiofex (1).

Another source of β -lactam resistance in MABS are the L,D-transpeptidases (Ldts). The better-studied D,D-transpeptidases (Ddts; also referred to as high-molecular weight penicillin-binding proteins or HMW PBPs) form 4,3-cross-links between adjacent peptidoglycan stem peptides. In contrast, Ldts form 3,3-cross-links, and in MABS, this linkage predominates. Ldts in MABS are resistant to penicillins but are inhibited by carbapenems and some cephalosporins. Important to the function of Ldts are the D,D-carboxypeptidases (D,D-c), a group of low-molecular-weight penicillin-binding proteins (LMW PBPs) that convert pentapeptides of peptidoglycan subunits to tetrapeptides that can subsequently be used by Ldts; these enzymes also appear to be inhibited by β -lactams.

It is believed that the synergy exhibited by dual β -lactams in susceptibility studies may be driven by inhibition of multiple enzymes in the peptidoglycan synthesis pathway (i.e., "target redundancy"). This "target redundancy" may lead to an unanticipated synergistic effect using β -lactam combinations. This hypothesis is supported by the finding that combinations of certain β -lactams and β -lactamase inhibitors inhibit more than one critical enzyme in the cell wall synthesis process. In addition to inhibition of Ldts, select cephalosporins and carbapenems are known to inhibit the traditionally recognized targets of β -lactams (Ddts) (2).

Dousa and colleagues have shown that durlobactam (DUR), a diazabicyclooctane (DBO) BLI, is an inhibitor of Bla_{Mab} and protects Bla_{Mab} substrates against hydrolysis but also exhibits intrinsic activity through inhibition of Ldts. Little is known about the potential role of sulbactam (SUL) against MABS, which does not inhibit Bla_{Mab} (2).

Dousa et al. suggest that DUR is a very potent inhibitor of Bla_{Mab} with an on rate kinetic constant 30-fold and 17,000-fold higher than was observed for the BLIs avibactam and relebactam, respectively. In cell-based assays, susceptibility of MABS isolates to amoxicillin (AMOX), IPM, and cefuroxime (CXM) was significantly enhanced with the addition of DUR. DUR combined with AMOX or CXM and IPM can inactivate multiple cell wall targets such as D,D-carboxypeptidase and two of the L,D-transpeptidases in MABS (Ldt_{Mab2,4}). The triple drug combinations of CXM-DUR-AMOX and IPM-DUR-AMOX were most potent, with Minimum Inhibitory Concentration (MIC) ranges of ≤ 0.06 to 1 $\mu\text{g/mL}$ and an MIC₅₀/MIC₉₀ of $\leq 0.06/0.25$ $\mu\text{g/mL}$, respectively (2). Shin et al (2025), performed time kill and enzyme kinetic studies using mass spectrometry which showed that DUR alone resulted in a $\sim 2 \log_{10}$ reduction in cell numbers, and when combined with IPM or two β -lactams, DUR achieved near-eradication of MABS (3). Enzyme kinetics were also favourable towards DUR.

Sulbactam-Durlobactam (SUL-DUR)

In vitro data support the efficacy of SUL-DUR against MABS in combination with orally available β -lactams (2, 4), and susceptibility testing of 50 clinical MABS strains from Australian patients with and without cystic fibrosis (CF) demonstrated similar results (unpublished data). β -Lactams are bactericidal, display overall excellent tolerability profiles and have been in use for decades. However, Bla_{Mab} contributes to β -lactam resistance. DUR is a novel BLI that inactivates Bla_{Mab} allowing β -lactams to destroy the bacterial cell wall. Other BLIs such as clavulanic acid and tazobactam are not active against Bla_{Mab}. Importantly, DUR has an advantage over other BLIs such as avibactam in that it has dual actions: a direct antibacterial effect on MABS in vitro (i.e. acts similarly to a β -lactam) plus inactivation of the β -lactamase that confers β -lactam resistance (2). The presence of DUR markedly decreases the MICs of AMOX and CXM against β -lactam-resistant MABS to levels which may render them effective at currently used doses. The addition of SUL-DUR to other β -lactams has been shown to enhance bacterial killing compared to the β -lactam alone (3, 5). Singh et al. have shown with a MABS hollow fibre infection model system that the SUL-DUR plus ceftriaxone combination was particularly potent, with a $3.85 \log_{10}$ reduction in bacterial burden without regrowth (5, 6). Ceftriaxone is widely available, generally well tolerated and achieves high lung concentrations. The biochemical rationale for including oral AMOX in the proposed treatment combination is to combine the β -lactam components to provide the best potential impact on MABS killing, as ceftriaxone and AMOX target different cell wall synthesis proteins thus, in combination with SUL-DUR achieving target redundancy and potentially significant synergy.

Arm D is also appealing as it will allow a reduction from three intravenous (IV) antibiotics to two IV antibiotics combined with oral agents with a potential reduction in toxicity.

Clinical use and tolerance of SUL-DUR

SUL-DUR has been approved by the U.S. Food and Drug Administration (FDA) for treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia in patients 18 years of age and older caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus* (*A. baumannii*) complex (7, 8).

The recommended duration of SUL-DUR is 7 to 14 days given by IV infusion over 3 hours, 4 times daily in adults with normal renal function. A preapproval expanded access program documented tolerability in a limited number of patients who received SUL-DUR for up to 42 days (9). The safety profile of SUL-DUR is based on a relatively small clinical development program in which the pivotal trial included only patients with serious hospital acquired bacterial pneumonia or ventilator associated bacterial pneumonia caused by *A. baumannii* (8). Adverse reactions occurring in the pivotal trial at a frequency of >5% were liver test abnormalities, diarrhea, anaemia, hypokalaemia, arrhythmia, acute kidney injury, thrombocytopenia, and constipation (8).

Advantages of SUL-DUR include:

- In vitro studies from different laboratories and different methodologies support the rationale of SUL-DUR.
- It is already FDA approved for serious respiratory infections.
- The pharmacokinetics of SUL-DUR is well described in the listed indication (Gram-negative pneumonia in critical care).
- It will reduce current intensive phase regimen from three IV agents to one or two IV agents with other companion drugs.
- Drug-drug interactions are unlikely to be problematic for most patients; there are no known drug-drug interactions with cystic fibrosis transmembrane conductance regulator (CFTR) modulators.
- It has a good safety profile observed in a highly vulnerable population with ventilator associated bacterial pneumonia and hospital acquired bacterial pneumonia making it likely to be better tolerated than the current standard of care (SOC) MABS treatment regimens.

2 PRIMARY OBJECTIVE ARM D

The primary objective of Appendix A3 is to determine if the β lactam/ β lactamase antimicrobial combination (Arm D) in the intensive phase of the trial will result in a greater proportion with MABS clearance with tolerance compared with 1) reference Arm A and 2) either of the remaining treatment arms detailed in Appendix A1 following the first interim analysis.

The primary outcome definitions, and secondary and exploratory objectives and outcomes are as per Appendix A1 Section 2.

3 DESIGN

Appendix A3 describes the intensive phase Arm D compared with each of the intensive treatment arms described in Appendix A1 (Figure 1).

Intensive Therapy Module

Appendix A3.1: Short Intensive Therapy: Arm D versus treatment arms detailed in Appendix A1 updated following the first interim analysis.

Appendix A3.2: Duration of Intensive Therapy for Patients with Ongoing Positive MABS cultures after completing 4 weeks vs 10 weeks of Intensive Therapy.

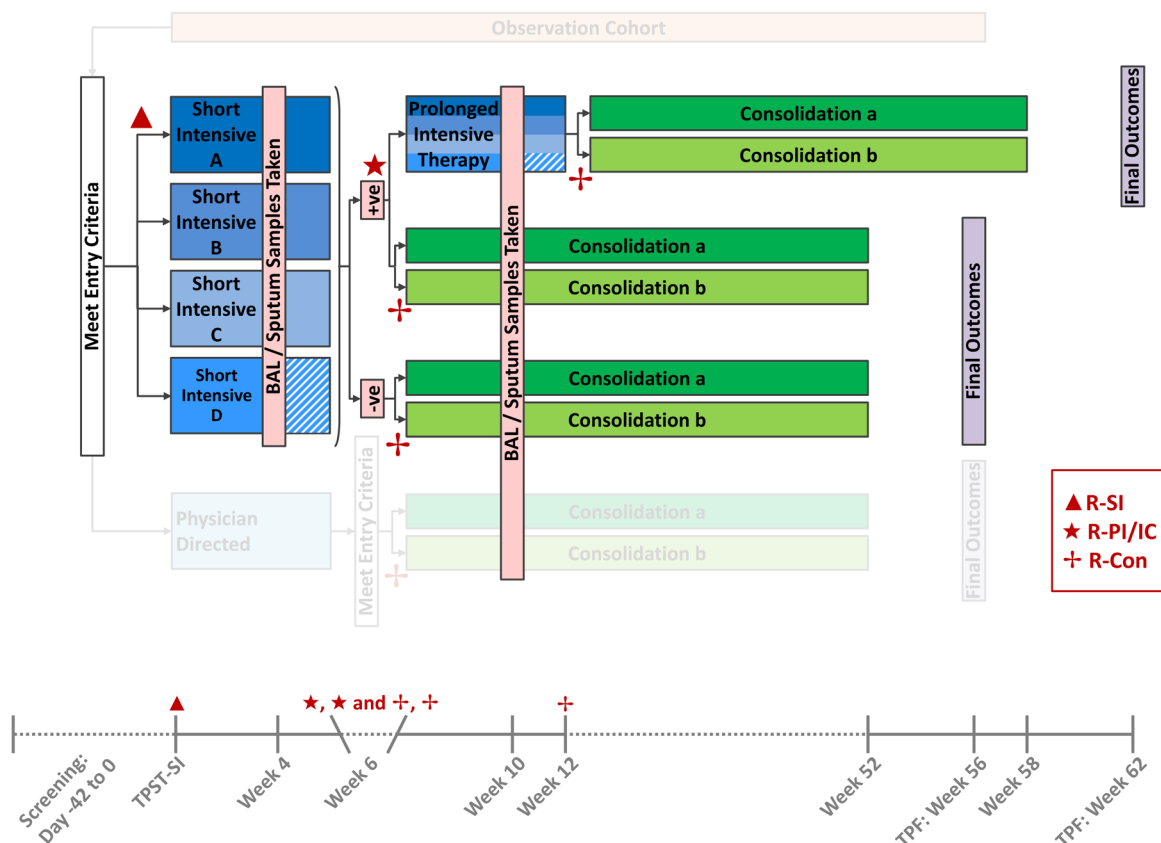


Figure 1 Flow Diagram for Appendix A1 and A3, Intervention Program Eligibility into the Intervention Program is determined at screening. At Randomisation-Short Intensive (R-SI) (▲); participants are randomised between the different intensive therapy arms (Intensive A, Intensive B, Intensive C or Intensive D) 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

Eligibility criteria for Appendix A3 are the eligibility criteria described in Master Protocol section 4.1, 4.2 and 4.4 and Appendix A1 section 4.1 and 4.3 with the additional inclusion and exclusion criteria detailed below.

4.1 INCLUSION CRITERIA

1. Inclusion criteria as described in Master Protocol section 4.2 and Appendix A1 section 4.1.
2. Male or female participants aged 12 years and older.

4.2 EXCLUSION CRITERIA

- Exclusion criteria as per Master Protocol section 4.2 and Appendix A1 section 4.2.
- Participants aged <12 years old.
- Participants aged between 12 and <18 years old with clinically significant renal impairment as indicated by an age-appropriate estimated creatinine clearance.
- Known hypersensitivity or contraindications to any of the therapies for which no alternative option(s) have been provided. This includes:
 - Sulbactam/durlobactam
 - Ceftriaxone,
 - Amoxicillin,
 - Macrolide antibiotics, and
 - Clofazimine.

4.3 ADDITIONAL CRITERIA

Additional criteria as per Master Protocol section 4.4 and Appendix A1 section 4.3.

5 ACCEPTABLE METHODS OF CONTRACEPTION

Acceptable methods of contraception for Appendix A3 are as described in Appendix A1 Section 5.

6 TRIAL CONDUCT

6.1 INFORMED CONSENT

Participants enrolling in Appendix A3 are required to sign and date the relevant Master Protocol and Appendix A consent(s). Consent will be obtained from participants or their parent/guardian in accordance with the policies described in section 5.4 of the FORMaT Master Protocol.

6.2 PREGNANCY INFORMATION CONSENT

Pregnancy Information Consent for Appendix A3 is as described in Appendix A1 Section 6.2.

6.3 METHODS OF ASSIGNING PARTICIPANTS TO TREATMENT ARMS

Participants will be randomised among 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. In this appendix, randomisation in the intensive phase (R-SI) will initially be in a 2:1:1 ratio between Arm D, the control Arm A, and the remaining intervention arm in Appendix A1 until the numbers of participants in each Arm have equalised (± 2), after which time the first interim analysis with Arm D will take place. Following the first interim analysis with Arm D, after a total of 100 participants have completed 6 weeks of intensive therapy, if appropriate, Bayesian Adaptive Randomisation (BAR) will be implemented for R-SI to adjust the allocation probabilities to favour the more promising intervention(s). BAR will then be used until the data support either early stopping for futility, or a maximum sample size is attained. R-PI between short or prolonged intensive for participants who remain culture positive at week 6 will be unchanged in a 1:1 ratio between short and prolonged intensive. As described in the Master Protocol, all randomisations will be conducted via Research Electronic Data Capture (REDCap) at each FORMaT 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.

Refer to Statistical Considerations in Appendix A3 and Appendix F: General Statistical Principles for detailed information regarding randomisation and statistical principles for Appendix A3.

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 as described in Appendix A1. 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 6 to 8. Toxicology thresholds will be defined in accordance with the Common Terminology Criteria for Adverse Events (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. All Intervention Program Procedures and Safety Monitoring for Appendix A3 are as described in detail in Appendix A1 Section 7.

8 SITE REIMBURSEMENT

For participants enrolled in Appendix A3, 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 A3.1: SHORT INTENSIVE THERAPY: THE USE OF INTRAVENOUS SULBACTAM – DURLOBACTAM IN COMBINATION WITH IV CEFTRIAXONE + ORAL AMOXICILLIN + ORAL MACROLIDE + ORAL CLOFAZIMINE DURING INTENSIVE THERAPY IN THE TREATMENT OF MABS-PD

Introduction

IV SUL-DUR, supplied in kind by Innoviva Specialty Therapeutics (IST), will be administered in combination with IV ceftriaxone, oral high dose amoxicillin, azithromycin and clofazimine for the treatment of MABS pulmonary disease (MABS-PD). This combination therapy will be delivered over a 4-week intensive period. During this respiratory samples will be collected according to the Schedule of Assessments. Following the 4-week intensive phase and while awaiting results and further randomisation at 6 weeks, participants will commence an oral only regimen. This treatment arm will be trialled in FORMaT participants aged ≥ 12 years, who are considered as adults for drug dosing purposes. IST are currently undertaking a paediatric study from birth to <18 years. Upon availability of safety data for the younger paediatric cohort, <12 years, FORMaT aims to extend the SUL-DUR containing arm to include these paediatric participants. Pharmacokinetic and pharmacodynamic studies will be required for both adult and paediatric participants for feasible sites able to participate in these studies.

At 6 weeks:

1. If respiratory samples remain culture positive for MABS they are randomised to either prolonged intensive (continuation of their previous intensive treatment regimen) or transition to consolidation therapy, with further randomisation to an oral only treatment or oral plus inhaled treatment.
2. If respiratory samples are negative for MABS, participants will continue on oral consolidation treatment and will be randomised to receive either, additional inhaled treatment or no inhaled treatment.

Eligibility Criteria

No additional eligibility criteria are required for participation in A3.1 from those described in Appendix A3, Section 4.

Objectives

Primary Objective

To compare the efficacy of Arm D against 1) reference Arm A and 2) either of the remaining treatment arms detailed in in Appendix A1 following the first interim analysis based 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).

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 bronchoalveolar lavage (BAL) sample collected at week 4.

Secondary Objectives

1. Microbiological clearance at 4 weeks (irrespective of toxicity) between Arm D and each of the treatment arms described in Appendix A1 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 Arm D compared to each of the treatment arms described in Appendix A1 in the short intensive therapy phase.
3. Change in FEV1 z-score at end of short intensive therapy versus at Screening with use of Arm D compared to each of the treatment arms described in Appendix A1.
4. Change in health-related quality of life (HRQoL) CF questionnaire – Revised (CFQ-R) for participants at end of short intensive therapy versus at Screening with use of Arm D compared to each of the treatment arms described in Appendix A1.
5. To examine general HRQoL between Screening and end of short intensive therapy in participants with use of Arm D compared to each of the treatment arms described in Appendix A1.
6. To examine the cost effectiveness of Arm D compared to each of the treatment arms described in Appendix A1 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 Arm D compared to each of the treatment arms described in Appendix A1.

Statistical Considerations

Sample size considerations: The schedule for interim analyses and stopping rules used in the trial and sample size for each research question was informed by simulations using Monte Carlo methods to give a range of power according to different plausible scenarios for responses to intensive interventions.

A simulation study was conducted to determine the study design and explore the statistical properties of adding Arm D into the intensive phase randomisation. While we cannot provide data on the primary outcomes by treatment arm, we have noted that approximately 30% of all participants have experienced poor tolerance during intensive therapy in the trial to date. We plan to drop one of the current treatment arms from the intensive phase at the first interim analysis due to feasibility, as guided by the independent data safety Finding the Optimal Regimen for *Mycobacterium abscessus* Treatment Appendix A3 Appendix A3-Intervention Program – Arm D, Version 1.0, Date 11 November 2025

monitoring board (iDSMB). Following this the new Arm D will be added. In the simulations, it is assumed that Arm-A (reference arm) will remain and either Arm B or Arm C will be dropped. For the purposes of the simulation, we assume Arm B continues, and Arm C is ceased. We simulated trials where 300 new participants are enrolled, along with 20 participants in Arm A and 20 participants from Arm B recruited (total 60 participants completed short intensive) prior to the new arm being added and assumed that interim analyses will be conducted after a total of 100 and subsequently after a total of 200 participants have been recruited and completed each phase (intensive and consolidation) of the trial. At these interim analyses the allocation ratio was updated using BAR based on the posterior probability of each intervention arm being better than control in terms of the primary outcome. The simulations allowed early stopping of an intervention arm for efficacy if the posterior probability of it being better than control is >99%, and for futility if the same posterior probability is <2% (these thresholds were chosen to provide desirable statistical properties in initial simulations). An intervention arm will be recommended if it stops early for efficacy or if there is evidence that the intervention is better than the control arm at the final analysis of 300 with a 1-sided p-value of 0.025. Simulations were repeated 100,000 times to estimate the type 1 error and power for 5 scenarios that varied:

- 1) The probability of clearance at R-SI for each of the 3 arms.
- 2) The probability of toxicity (lack of tolerability) at the R-SI for each of the 3 arms.

In all cases it was assumed that 10 participants per month were enrolled to the intensive phase and that the probability of toxicity and clearance are independent. The below table shows the outcomes and operating characteristics for the five scenarios (*Represents false positive rate rather than power):

Scenario	Probability of clearance at intensive phase (Arm A, B, D)	Probability of toxicity at intensive phase (Arm A, B, D)	Power to conclude intervention Arm D better than A	Proportion of replicates where Arm D stops early for efficacy
1	(0.66,0.66,0.66)	(0.3,0.3,0.3)	0.033*	0.017
2	(0.66,0.66,0.75)	(0.3,0.3,0.1)	0.93	0.64
3	(0.66,0.7,0.75)	(0.3,0.2,0.1)	0.90	0.61
4	(0.66,0.66,0.8)	(0.3,0.3,0.1)	0.99	0.83
5	(0.66,0.66,0.9)	(0.3,0.3,0.1)	>0.99	0.99

Scenario 1 represents the ‘null scenario’ where no intervention makes a difference to outcomes.

Scenario 2 assumes that Arm D makes a small difference to clearance and a larger difference to toxicity. Scenario 3 is the same as scenario 2 other than Arm B is assumed to have modest effect on toxicity and clearance (thus meaning the BAR procedure will allocate fewer individuals to Arm D on average). Scenario 4 is the same as scenario 2 but it assumes a larger effect of Arm D on clearance. Scenario 5 is the same as scenario 4 other than it assumes an even larger effect of Arm D on clearance. The sample size of 300 with

interim analyses at 100 and 200 participants provides 99% power if the new intensive arm provides an improvement in the probability of clearance with tolerance from 66% in the control arm to 80% in Arm D. With this scenario, there is an 83% chance that the new intensive arm would stop early for efficacy.

Statistical methods: The interim and final analyses will be conducted using a Bayesian logistic regression model for the primary outcome adjusted for stratification factors. Once an arm is stopped (either at an interim analysis or at 300 participants) a frequentist analysis will also be conducted and reported along with data on the secondary outcomes. All analyses will be conducted using the intention to treat/treatment policy principle. The statistical analysis will also explore the best treatment strategies (linking intensive phase with consolidation phase) using methodology for analysing Sequential Multi Assignment Randomised Trials (10) as detailed in Appendix F General Statistical Principles.

10 INTENSIVE THERAPY DOSING REGIMEN

At R-SI, participants will be randomised to either Arm D or the treatment arms outlined in Appendix A1 during the intensive phase. Participants randomised to Arm D will receive drug therapy in accordance with the dosing tables below. Drug therapy, administration and duration is dependent on the treatment arm the participant is randomised to. 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.

R-SI dictates the drug therapy that participants will be randomised to.

Intensive Arm D	
Weeks 1 to 4 (and Weeks 7 to 10 if randomised to prolonged intensive therapy)	Weeks 5 to 6 (and Weeks 10 to 12 if randomised to prolonged intensive therapy)
<ol style="list-style-type: none"> 1. IV sulbactam-durlobactam 2. IV ceftriaxone 3. Oral amoxicillin 4. Oral azithromycin or clarithromycin 5. Oral clofazimine 	<ol style="list-style-type: none"> 1. Oral clofazimine, and; 2. Oral azithromycin or clarithromycin, and; 3. In combination with one to three of the following oral antibiotics: <ul style="list-style-type: none"> • Linezolid, • Trimethoprim / sulfamethoxazole (co-trimoxazole), • Bedaquiline, • Rifabutin. • Doxycycline • 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 Arm D intensive therapy dosing regimen tables outlined below are separated by age (adult, paediatric). The recommended doses and frequencies are a guideline and participant dosing must also take into account clinical judgement, the Investigator's Brochure (for SUL-DUR) and relevant prescribing information for the non-SUL-DUR drugs in Arm D.

The medications in Arm D have the potential for drug-drug interactions. The clinician should consider drug and non-drug interactions, special warnings and precautions for use prior to prescribing these medications according to the Investigator's Brochure (for SUL-DUR) and relevant prescribing information for the non-SUL-DUR drugs in Arm D.

Table 1 Intensive therapy dosing regimen for Intensive Arm D in adults – WEEKS 1 to 4 (and WEEKS 7 to 10 if randomised to prolonged intensive therapy)

WEEKS 1 to 4 Intensive Arm A: Adult Dosing^A		
Drug	Recommended Dose (per dose)	Frequency
IV sulbactam-durlobactam	Greater than or equal to 130ml/min	Every FOUR (4) hourly. Administered by intravenous infusion over 3 hours.
	For CrCL 45 to 129ml/min 1g sulbactam/ 1g durlobactam	Every SIX (6) hourly. Administer by intravenous infusion over 3 hours.
	For CrCL 30 to 44ml/min 1g sulbactam/ 1g durlobactam	Every EIGHT (8) hourly. Administer by intravenous infusion over 3 hours.
	For CrCL 15 to 29ml/min 1g sulbactam/ 1g durlobactam	Every TWELVE (12) hourly. Administer by intravenous infusion over 3 hours.
	For CrCL<15ml/min 1g sulbactam/ 1g durlobactam	Every TWELVE (12) hourly for first 3 doses then reduce to every 24 hourly thereafter. Administer by intravenous infusion over 3 hours.
IV ceftriaxone	1g	Every TWELVE (12) hourly
Oral amoxicillin	1000mg	Three times daily
Oral azithromycin	250 – 500mg	Once daily
<i>If azithromycin not tolerated, use oral clarithromycin.</i>	<40kg or poorly tolerated 250mg	Once daily
Oral clarithromycin <i>Clarithromycin only for use if azithromycin not tolerated.</i>	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)	Once daily
	OR 25mg/kg (rounded to account for tablet strength)	Thrice weekly

^A The recommended doses and frequencies are a guideline and participant dosing must also consider clinical judgement, the Investigator's Brochure (for SUL-DUR) and relevant prescribing information for the non-SUL-DUR drugs.

Table 2 Intensive therapy dosing regimen for Intensive Arm D in paediatrics (aged 12 years and older) – WEEKS 1 to 4 (and WEEKS 7 to 10 if randomised to prolonged intensive therapy)

WEEKS 1 to 4 Intensive Arm D: Paediatric Dosing ^A			
Drug		Recommended Dose (per dose)	Frequency
IV sulbactam/durlobactam		Sulbactam 25mg/kg Durlobactam 25mg/kg Do not to exceed 1g sulbactam - 1g durlobactam	Every SIX hourly. Administer by intravenous infusion over 3 hours.
IV ceftriaxone		1g	Every TWELVE (12) hourly
Oral amoxicillin		1000mg	Three times daily
Oral azithromycin <i>If azithromycin not tolerated, use oral clarithromycin.</i>		10mg/kg, max 500mg	Once daily
Oral clarithromycin <i>Only for use if azithromycin not tolerated.</i>	Children 1 month – 11 years of age		Twice daily
	<8 kg	7.5mg/kg	
	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 ----- ≥40kg 100mg	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, the Investigator's Brochure (for Sul-Dur) and relevant prescribing information for the non-Sul-Dur drugs.

Table 3 Intensive therapy dosing regimen in adults – WEEKS 5 to 6 (and WEEKS 7 to 10 if randomised to prolonged intensive therapy)

WEEKS 5 to 6 Intensive Therapy Arm-D: Adult Dosing^A		
Drug	Recommended Dose (per dose)	Frequency
Oral clofazimine	100 – 300mg	Once daily
Oral azithromycin <i>If azithromycin not tolerated, use oral clarithromycin.</i>	250 – 500mg OR 500mg	Once daily Thrice weekly
	<40kg or poorly tolerated 250mg	Thrice weekly
Oral clarithromycin <i>Clarithromycin only for use if azithromycin not tolerated.</i>	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 <i>(Weighing at least 30kg)</i>	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	Once daily
	25mg/kg (round to account for tablet strength)	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 in paediatrics – WEEKS 5 to 6 (and WEEKS 7 to 10 if randomised to prolonged intensive therapy)

WEEKS 5 to 6 Intensive Therapy Arm-D: 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 ≥40kg 100mg	Once daily
Oral azithromycin <i>If azithromycin not tolerated, use oral clarithromycin.</i>		10mg/kg, max 500mg	Once daily
Oral clarithromycin <i>Only for use if azithromycin not tolerated</i>	Children 12 to <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.

10.1.1 DRUG SUPPLY, STORAGE AND DISTRIBUTION DURING INTENSIVE THERAPY

Sulbactam-Durlobactam

Shipping, clinical trial drug labelling, storage prior to delivery to trial sites and distribution to trial sites will be the responsibility of the FORMaT Sponsor and their contracted vendor(s). The supply of SUL-DUR will be provided in-kind by the industry partner IST. Trial sites will be responsible for the storage, accountability, dispensing and administration of SUL-DUR at their respective trial site. Trial sites will be responsible for the destruction of SUL-DUR at the Sponsor's request.

Other non-SUL-DUR drugs in Arm D

Supply, distribution and storage of the non-SUL-DUR drugs within Arm D will be the responsibility of the investigational site, utilising site/institutional pharmacy stock. These activities will be conducted as per standard of care and in accordance with site specific policies and regulatory requirements.

Any medication the participant is prescribed which are not investigational products, including adjunctive treatments, for example, medication to treat nausea, will be commercially available products and are to be sourced and supplied locally by study sites according to local standard practices.

10.1.2 OPTIONS FOR REDUCING NAUSEA DURING INTENSIVE THERAPY

Study drugs used in the intensive phases of the FORMaT Trial may cause nausea. Pharmacological treatment options to manage nausea are at the discretion of the clinician and are to be prescribed according to local guidelines.

11 SCHEDULE OF ASSESSMENTS

Table 5 lists the special considerations that are applicable to all Schedule of Assessment tables. Table 5 must be used in conjunction with Tables 6 to 8. Tables 6 to 8 show the schedules of assessment tables for participants enrolled in Appendix A3. Table 6 shows the schedule of assessments for all participants from Screening to end of Week 6, Table 7 shows the schedule of assessments from Week 7 to Week 12 for participants randomised to Prolonged Intensive and Table 8 shows the schedule of assessments for all participants during the Consolidation therapy phase and at the Final Outcome. Acceptable study visit windows are also outlined in tables 6 to 8.

Table 5 Special considerations for Schedule of Assessments

Symbol	Definition
A	Participant reconsent is required with Institutional Review Board/ Independent Ethics Committee /Human Research Ethics Committee (IRB/ IEC/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 Appendix A1 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 Appendix A1 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.
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 Short Form-36 (SF-36) health survey 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 Pediatric Quality of Life Inventory (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 St George Respiratory Questionnaire (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	5-item Medication Adherence Rating Scale (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 FORMaT 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.
2	Vital signs to be performed: Heart rate (pulse), blood pressure, respiratory rate and body temperature.

Table 6 Schedule of Assessments for Intervention Program Participants in Appendix A3: Intensive Therapy (Screening and first six weeks of intensive therapy)

ASSESSMENT		SCREENING VISIT	INTENSIVE THERAPY					
		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 6 ±3 Days
Informed consent for Appendix A3 ^A		✓						
Clinic visit ^B		✓	✓	✓	✓	✓	✓	✓
Review eligibility		✓						
Randomisation			✓					✓
Adverse event monitoring			✓	✓	✓	✓	✓	✓
Respiratory sample	Sputum (expectorated or induced) <i>or</i> ;	✓ ^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						
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					✓
Vital signs ²		✓		✓	✓	✓	✓	
Health-related quality of life questionnaires:								
1. EQ-5D-5L or -Y ^N		✓						✓
2. SF36 ^O		✓						✓
3. PedsQL ^{TM P}		✓						✓
4. CFQ-R ^Q		✓						✓
5. Child Health Utility 9D ^R		✓						✓
6. SGRQ ^S		✓						✓
Costs Questionnaire		✓						✓
Medication Adherence Questionnaire ^U								✓

Table 7 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 12 ±3 Days
Clinic visit ^B		✓	✓	✓	✓	✓
Randomisation						✓
Adverse event monitoring		✓	✓	✓	✓	✓
Respiratory sample	Sputum (expectorated or induced) <i>or</i> ;				✓x3 ^W	
	BAL				✓ ^W	
Height ^E and Weight						✓
Medication Review		✓	✓	✓	✓	✓
Spirometry						✓
Chest CT						Optional ^V
Pregnancy Test and Breastfeeding Status ^H				✓		✓
ECG ^J						✓
6-minute walk test ^K						✓
Blood collection:						
7. Chemistry and Renal Function		✓	✓	✓	✓	✓
8. Liver Function Tests		✓	✓	✓	✓	✓
9. Full Blood Count		✓	✓	✓	✓	✓
Physical examination						✓
Vital Signs ²		✓	✓	✓	✓	
Health-related quality of life questionnaires:						
10. EQ-5D-5L or -Y ^N						✓
11. SF36 ^O						✓
12. PedsQL ^{TM P}						✓
13. CFQ-R ^Q						✓
14. Child Health Utility 9D ^R						✓
15. SGRQ ^S						✓
Costs Questionnaire						✓
Medication Adherence Questionnaire ^U						✓

Table 8 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 n (Week 52) +5 days	Week 18 ±30 days	Week 28 ±30 days	Week 38 ±30 days	End of consolidation n (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) <i>or</i> ;	✓ x3 ^W		✓ ^X	✓ ^X	✓ ^X	✓ ^X	✓ ^X	✓ ^X	✓ ^X	✓ ^Y	✓	
	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											✓	✓	
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 APPLICABLE DISCOVERY STUDIES AND REGISTRY LINKAGE FOR APPENDIX A3

Intervention Program participants in Appendix A3 may be eligible to enrol in the following FORMaT Sub-Studies and Integrated Studies:

- 1) Appendix C Discovery
 - i. C1: Pharmacokinetics
 - i) C1.3 Pharmacokinetics of MABS-PD therapies
 - ii) C1.4 Pharmacokinetics of CFTR modulator therapy in persons with CF on MABS therapy
 - iii) C1.5 Pharmacokinetics of SUL-DUR
 - 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.

13 REFERENCES

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