Appendix 1. Pilot trial IBMFRS data

The MEANS Procedure

TREATMENT GROUP=A

Variable	Label	N	Mean	Std Dev	Minimum	Maximum
IBMFRSSC	IBMFRS AT SCREENING	22	32.3181818	3.5103434	24.0000000	37.0000000
IBMFRS0	IBMFRS AT BASELINE	22	32.2272727	4.0582874	20.0000000	37.0000000
IBMFRS6	IBMFRS AT MONTH 6	22	33.0909091	4.6281652	21.0000000	39.0000000
IBMFRS12	IBMFRS AT MONTH 12	22	31.1818182	4.2047180	22.0000000	38.0000000
DIBMFRS6	6-MONTH CHANGE IN IBMFRS	22	0.8636364	2.8333970	-6.0000000	6.0000000
DIBMFRS12	12-MONTH CHANGE IN IBMFRS	22	-1.0454545	3.6315715	-8.0000000	9.0000000

TREATMENT GROUP=B

Variable	Label	N	Mean	Std Dev	Minimum	Maximum
IBMFRSSC	IBMFRS AT SCREENING	22	29.6818182	6.2821468	9.0000000	38.0000000
IBMFRS0	IBMFRS AT BASELINE	22	30.1363636	6.5049099	9.0000000	38.0000000
IBMFRS6	IBMFRS AT MONTH 6	21	29.5714286	7.8649312	6.0000000	40.0000000
IBMFRS12	IBMFRS AT MONTH 12	22	27.2272727	7.5462499	8.0000000	39.0000000
DIBMFRS6	6-MONTH CHANGE IN IBMFRS	21	-0.5714286	6.7421913	-12.0000000	21.0000000
DIBMFRS12	12-MONTH CHANGE IN IBMFRS	22	-2.9090909	5.5369675	-17.0000000	5.0000000

Appendix 2. Study eligibility criteria

Inclusion criteria

Adults who meet **all** the following criteria may be included in the study:

1. Adults able to read and understand the Participant Information Sheet, and who freely provide written Informed Consent for the study;
2. Males or females aged 45 years or older;
3. Diagnosis of IBM according to the criteria proposed by the ENMC criteria 2011;
4. Able to walk a minimum distance of 200m and maximum distance of 500m within 6 minutes (walking aids, including frames, may be used);
5. Evidence of disease progression over the previous 12 months, as determined by a neuromuscular specialist through patient history, physical examination, MMT, IBM-FRS or other metrics.

Exclusion criteria

Any of the following will exclude potential patients from the study:

1. Inability to complete a 6MWT with a minimum distance of 200m and maximum distance of 500m achieved;
2. Inability to complete a mTUG or any other study procedure, including inability to swallow study drug, or clinical suspicion that the participant will become unable to swallow the study drug during the study period;
3. Unwillingness or inability to comply with study interventions or study schedule;
4. Hypersensitivity to Sirolimus, everolimus or any compound of the oral solution;
5. Any prior exposure to Sirolimus or everolimus within the last 6 months;
6. Presence of any other clinically significant disease that might interfere with patients' ability to comply with study procedures, or places the patient at greater risk for SAEs;
7. Clinical suspicion of moderate *or* severe respiratory insufficiency based on history, clinical examination or respiratory function tests with an FVC < 50% of predicted; Nocturnal NIV is allowed for sleep-disordered breathing;
8. Severe chronic kidney disease or renal insufficiency with proteinuria (*e.g.*, estimated glomerular filtration rate < 30 ml/min and/or proteinuria as defined by spot urine protein/creatinine ratio > 100mg/mmol;
9. Chronic liver disease (cirrhosis and/or ALT/AST > 3 times the upper limit of normal (ULN)), excluding cases in which raised ALT/AST are deemed to be due to underlying muscle disease. Patients can be re-screened within the window if a one-off measurement is elevated due to an acute injury such as a viral infection;
10. History of cancer (except localised skin cancers including BCC/SCC) during the past 5 years;
11. Systemic autoimmune or rheumatological disease not in remission and/or necessitating specific treatment during the last 12 months. This includes significant organ-specific autoimmune disorder (*e.g.*, Grave's disease) not in remission and/or necessitating specific treatment during the past 12 months;
12. Any unhealed wounds or active infections at the time of screening;
13. If patient has received a live vaccine within the last 12 weeks;
14. Participants must be HIV negative, and Hepatitis C Virus (HCV) antibody negative or Polymerase Chain Reaction (PCR) negative, and Hep B surface antigen negative and Hep B core antibody negative;
15. One or more the following blood test results at screening:

a. Total cholesterol > 8 mmol/l (304mg/dl)
b. Triglycerides > 5 mmol/l (>194 mg/dl)
c. Haemoglobin < 110 g/L (11g/dl)
d. Platelet count < 100 x 109/L
e. Neutrophils < 1.5 x 109/L
f. Lymphocytes < 1.0 x 109/L

16. Presence at screening of any medically significant cardiac, neurological, pulmonary, gastrointestinal, musculoskeletal or psychiatric illness (including uncontrolled anxiety and/or depression) that in the Investigator's opinion might interfere with the patient's ability to comply with study procedures or that might confound the interpretation of clinical safety or IBM-FRS;
17. Suspected or known presence of VCP mutation, as assessed by family history of Paget's Disease and/or fronto-temporal dementia and/or myopathy, and/or an unexplained persistently elevated ALP. If there is any suspicion of a VCP mutation, this should be confirmed by formal genetic analysis prior to enrolment.
18. Has taken any investigational study drug within 30 days or five half-lives of the prior agent (whichever is longer) prior to the Baseline visit;
19. Patient taking any other immunosuppressive or immunomodulatory medication (including but not limited to prior high dose prednisolone (>10mg/day) in the last 4 weeks, Intravenous Immunoglobulin (IVIG) within the last 3 months, methotrexate, mycophenolate, sirolimus, everolimus, calcineurin inhibitors, (cyclosporine or tacrolimus) or azathioprine within the last 6 months, and rituximab, alemtuzumab or other biologics within the last 12 months);
20. Other medications or products that may affect the metabolism of Sirolimus (See concomitant medications in Section 27) such as the following at time of screening:

a. Strong inhibitors of CYP3A4 and/or P-gp (*e.g.,* ketoconazole, voriconazole, itraconazole, telithromycin, erythromycin or clarithromycin)
b. Strong inducers of CYP3A4 and/or P-gp (*e.g.,* rifampicin, rifabutin, Phenytoin, Phenobarbitol, St John's Wort);

21. Pregnancy or planning a pregnancy:

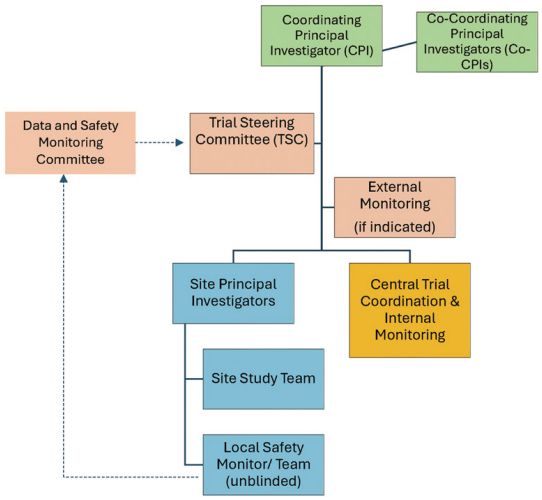
a. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test prior to randomisation, and must have a negative urine pregnancy test within 24 hours prior to the start of study drug. WOCBP must agree to use 'highly effective' contraception (MHRA guidelines, 2014) for the duration of the study and for 12 weeks post-treatment completion.
b. Men who are sexually active with a WOCBP must agree to use barrier contraception (condom) for the duration of treatment with study drug and for 30 days post-treatment completion.

22. COVID vaccination within last 4 weeks.

Appendix 3. Study schedule of events.

Visit	Screening	Baseline Visit 1	Safety bloods	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Follow-up Visit 10	Early termination
Week	-	**0**	**Day 10**	**4**	**12**	**24**	**36**	**52**	**64**	**76**	**84**	**88**	**-**
Informed consent	X												
Inclusion/exclusion criteria	X	X											
Medical history	X												
Physical exam	X	X		X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X
Vital signs	X	X		X	X	X	X	X	X	X	X	X	X
Height	X												
Weight	X	X		X	X	X	X	X	X	X	X	X	X
Haematology	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid profile	X	X			X			X			X		X
Sirolimus level			X	X	X	X	X	X	X	X	X	X	X
Hep B/C, HIV test	X												
Pregnancy test	X (serum)	X		X	X	X	X	X	X	X	X	X	X
Mid-stream urine: protein/creatinine ratio	X			X									
Urinalysis	X	X		X	X	X	X	X	X	X	X	X	X
Drug capsule swallowing trial	X												
IBM-FRS		X			X	X		X		X	X		X
PROs		X			X	X		X		X	X		X
mTUG	X	X			X	X		X		X	X		X
6MWT (2MWT)	X	X			X	X		X		X	X		X
QMT – Quads + Hand Grip + Pinch Grip (Citec)		X			X	X		X		X	X		X
MMT8, MMT8 IBM, MMT12		X				X		X			X		X
Central laboratory blood samples (DNA + Serum)		X											
Dispense study drug		X		X	X	X	X	X	X	X			
Drug accountability				X	X	X	X	X	X	X	X		X
Adverse events and review of study diary		X	X	X	X	X	X	X	X	X	X	X	X

Appendix 4. Organisational structure and responsibilities.



Coordinating Principal Investigator (CPI)
- Responsible for design and conduct of study
- Preparation of protocol and revisions, submission to Lead Human Research Ethics Committee (HREC)
- Preparation of Case Report Forms (CRF) and Manual of Procedures (MOP)
- Organisation of Trial Steering Committee (TSC)
- Trial coordination oversight
- Publication of study reports for Sponsor and governance/regulators

Co-Coordinating Principal Investigators (Co-CPI)
- Deputises for the CPI
- Responsibilities as per CPI

Trial Steering Committee (TSC)
- Protocol approval
- Recruitment strategy and review
- Reviewing progress of study and agree changes to the protocol to facilitate study delivery

Data Safety and Monitoring Committee (DSMC)
- Organisation of regular data and safety meetings, as per monitoring plan
- Independent review of safety and data reports
- Serious adverse event (SAE) and Suspected Unexpected Serious Adverse Reaction (SUSAR) review
- Identify any recommendation for stopping trial due to safety or data signals

External Monitoring (if indicated, as per Study Monitoring Plan)
- Electronic Data Capture (EDC) and source document monitoring as required
- Site compliance review/audit as required
- Quality and assurance processes as required

Central Trial Coordination & Internal Monitoring
- Study coordination
- Site Initiation Visits (SIV) (remote), including study training and regulatory approvals
- Responsible for Trial Master File (TMF)
- Budget administration and contracts with study sites
- Advice for Site Principal Investigators and site teams
- Assistance with international review, board/independent ethics committee applications
- Development and maintenance of trial IT system (EDC)
- Coordination of IP supply

Site Principal Investigators
- Outside of Australia, site PI's will act as the Sponsor Representative at their site
- Responsible for site ethics and governance submissions, regulatory approvals
- Responsible for participant identification, recruitment, data collection and completion of eCRFs
- Responsible for participant safety at site and safety reporting, including AE reports
- Reporting of SAEs or SUSARs to CPI and Sponsor, as per protocol

Site Study Teams
- Study set-up and approvals at site, including local site contracts
- Liaison with local providers, including pharmacy and biochemistry
- Recruitment and study visits
- Maintenance of site files
- Local study team training and quality control
- Data entry and data management
- SAE and SUSAR reporting
- IP dispensing and accountability at site

Local Safety Monitor / Team
- Review of local study safety bloods (as specified in site safety monitoring plan)
- Reporting of SAEs to Site PI, CPI and Sponsor as required
- Dose modification as required
- Emergency unblinding
- Reporting to DSMC and membership of DSMC