Optimism in inclusion body myositis: a double-blind randomised controlled phase III trial investigating the effect of sirolimus on disease progression in patients with IBM as measured by the IBM Functional Rating Scale

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Abstract

Objective

Inclusion body myositis (IBM) is a complex inflammatory muscle disease in adults over 40, with histological features of autoinflammation, cell stress and autophagic abnormalities, and marked clinically by relentless progression with no effective disease-modifying therapy. Sirolimus (rapamycin) may help maintain function by inhibiting T effector cells, preserving T regulatory cells, inducing autophagy, and improving mitochondrial function. This international trial follows a phase II pilot study.

Methods

This phase IIb/III double-blind, randomised, controlled trial (RCT) of sirolimus involves 140 IBM patients randomly assigned with equal allocation to sirolimus (2 mg) or matching placebo. This RCT aims to assess the efficacy of sirolimus compared to placebo in slowing or stabilising IBM progression, as measured by the mean change in patient function using the IBM Functional Rating Scale (IBM-FRS) from Baseline to Week 84. Secondary outcomes will evaluate efficacy and safety to inform future clinical trial design.

Results

Ethical approval has been granted in Australia (St Vincent's Hospital Melbourne HREC-D 311/20) and the USA (University of Kansas Medical Center Human Research Protection Program FWA no. 00003411), with European approval pending. The protocol is version 3.0 (02-Dec-2022). Trial registration: ANZCTR: ACTRN12620001226998p, ClinicalTrials.gov: NCT04789070, UTN: U1111-1258-1354, and EU CT 2024-514575-17-00.

Conclusion

This phase IIb/III trial builds on prior findings to assess sirolimus's potential in slowing or halting IBM progression, preserving patient function and independence, and advancing IBM therapeutic strategies and trial design.

Key words

clinical trials, inclusion body myositis, international, investigator-inititated

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Introduction

Study rationale and evidence gap

Inclusion body myositis (IBM) is the most common inflammatory myopathy in patients over 40 years. Its prevalence is reported to be 16-70 per million in Caucasian general populations, and recently reported in a US study as 180 per million in people ≥50 years old (1, 2). Men are affected twice as commonly. It is a relentlessly progressive disease untreatable by traditional immunosuppressive or immunomodulating agents. It leads to severe muscle weakness and disability, and ultimately dependence and even death. Therefore, there is an urgent need for a treatment that slows disease progression. Histopathologically the key features are a combination of inflammation, seen by an inflammatory infiltrate by $CD8^+$ T-cells; MHC-I and MHC-II expression on myofibres; and degenerative changes, seen by vacuolar changes and accumulation of many different proteins including p62 and TDP43, thought to reflect impaired protein homeostasis, as well as accelerated mitochondrial dysfunction. Whilst the aetiopathogenesis is unclear, both the inflammatory and degenerative processes are thought to contribute to the progressive muscle loss, weakness and disability experienced by IBM patients, although there is mounting evidence in favour of IBM being primarily an autoimmune disease mediated by terminally differentiated treatment resistant T cells (3).

Immunopathogenesis of IBM

The inflammatory changes in IBM muscle comprise a $CD8^+$ T cell predominant infiltrate with invasion of non-necrotic muscle fibres and diffuse sarcolemmal up-regulation of MHC-I and II molecules, implying that the muscle fibres are acting as antigen-presenting cells. The inflammatory changes are more prominent early in the disease (4), whereas autophagic vacuoles and other degenerative changes become more prominent as the disease progresses. IBM has a very strong HLA association with the 8.1 ancestral haplotype (also known as the autoimmune haplotype), and occurs in association with other autoimmune conditions such as Sjögren's disease in 13–24% of cases (5). It can also occur in the context of immunodeficiency disorders and chronic viral infections including human immunodeficiency virus and human T-cell leukaemia virus, suggesting that chronic viral infection with immune recognition is sufficient to trigger this inflammatory myopathy (6). The invasive $CD8^+$ T cells are clonally expanded as indicated by a limited diversity in the CDR3 region of the T cell receptor that persists in serial biopsies, also implying an antigen-driven immune response (7, 8). More recently, 58% of IBM patients were found to have an expanded $CD8^+$ T cell population, compatible with T cell large granular lymphocytic leukaemia (TLGL); these cells display high levels of CD57, a marker of persistent T cell exposure to antigen and T cell aggressiveness (9). These terminally-differentiated T cells express high levels of cytotoxic perforin and granzymes overlapping phenotypically and functionally with natural killer cells. In addition, IBM patients have higher levels of Th1-associated cytokines (such as interferon-γ (IFNy)) and chemokines than controls. The $CD8^+CD28$- T cells that have escaped co-stimulatory control are the major producers of IFNγ. Importantly, in IBM there is a deficiency of circulating regulatory T cells (Treg) (10), thought to be protective against autoimmunity. There is also evidence of a humoral immune component, with a third to half of cases associated with a circulating auto-antibody directed against cytosolic-5'-nucleotidase 1A (CN1A) (11, 12).

Potential role for sirolimus: combating both degenerative and inflammatory processes

Sirolimus is a currently licensed drug primarily used for immunosuppression post-kidney transplantation to prevent organ rejection. Sirolimus was initially considered as a treatment in IBM for its immunosuppressive action and beneficial effects in an experimental myositis mouse model (13). Transfer of effector T cells from affected to healthy animals resulted in myositis, but the presence of Treg cells was protective against development of myositis (11).

As sirolimus, which acts to deplete effector T cells but preserves the Treg cells, was effective in this mouse model of myositis, it was therefore postulated that it may also be effective in IBM, not only for its effects on effector T cells and Treg cells, but also for its additional effects on protein degradation.

Sirolimus also inhibits mammalian target of rapamycin (mTOR) that is considered a "master switch" or central regulator of cell growth and proliferation. When the mTOR C1 pathway is activated, it increases protein and energy production, aids healing and encourages muscle growth (14). On the other hand, inhibition of mTOR increases autophagy, the process by which damaged or ineffective proteins are removed from cells. There is evidence of impaired autophagy in IBM (15, 16).

Therefore, sirolimus is "currently the most effective and reproducible pharmacological approach for directly targeting the aging process to increase life span and health span in laboratory animals" (17), and has been trialled for other diseases associated with aging and protein accumulation/deposition including amyotrophic lateral sclerosis (ALS) (18) and Parkinson's disease (19). It has also been trialled in older adults and shown to be safe in this aging population (20).

In summary, IBM is a muscle disease associated with aging with evidence of: (a) excessive protein deposition in muscle cells, (b) abnormal mitochondrial function, (c) reduced muscle regeneration, (d) reduced Treg cells, and (e) clonal expansion of effector T cells. We hypothesise that inhibition of mTOR by sirolimus may slow the disease progression by blocking the activity of T effector cells but preserving T regulatory cells, as well as by inducing autophagy (protein degradation). This phase III trial will directly test this hypothesis.

Preliminary study

A previous single-centre pilot RCT comparing Sirolimus with placebo was conducted in Paris, France (NCT02481453) (21). Forty-four patients were treated with oral sirolimus (2mg/d, n=22) or placebo (n=22) over 12 months, followed by an open-label extension. Sirolimus was well tolerated in the pilot study. The IBM-FRS score was relatively stable in the sirolimus group, changing by a mean of -1.38% (SD 13.78%), *vs*. a mean change of -8.84% (SD 17.79%) in the placebo group (p=0.14). The 6-minute walk distance (6MWD) was stable in the treated group (mean change: -4.1 m *vs*. -38.5 m, p=0.035), IBM weakness composite index was less degraded (11.91% *vs*. 24.26%, p=0.038) and forced vital capacity significantly improved (mean relative change: +12.3% *vs*. 1.6%, p=0.016). Additionally, quantitative magnetic resonance imaging (MRI) showed significant less change in fat muscle replacement in quadriceps (1.7% *vs*. 4.4%, p=0.025) and hamstrings (0.9% *vs*. 7.3%, p=0.027). Finally in MRI, the loss of contractile cross-sectional area (mm^2) was less pronounced in the sirolimus group in quadriceps (-3.7 *vs*. 10.7, p=0.005). Notably, for one of the only times in a RCT in IBM, an improvement of the 6MWD was observed. Our aim is to confirm these positive pilot single-center results in an independent international cohort of patients.

Justification for a larger multicentre confirmatory study

Results from the pilot study are encouraging, and sparked interest in confirmation of these data in larger multicentre study. Contributing to the rationale for this proposed confirmatory trial is the fact that the investigators from the pilot study have extended sirolimus treatment for their initial cohort, making it essential (with respect to for example generalisability, safety and efficacy) for other centres to validate and confirm their preliminary findings. Sirolimus is an established Therapeutic Goods Administration (TGA) Australia, United States of America Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved drug, diminishing financial and regulatory hurdles to translating the results in IBM care globally. Sirolimus is well-known by medical practitioners, who have experience with dose management and monitoring of patients on this therapy. Finally and most importantly, we have an obligation to pursue this potential treatment to determine whether it can slow or stabilise disease progression in patients with IBM.

Methods and analysis

Study design

This is an 88-week, phase III, randomised, double-blind, placebo-controlled, international multicentre study in participants with IBM to assess the clinical efficacy and safety of sirolimus compared to placebo in slowing or stabilising disease progression, as measured by the changes in the IBM-FRS total score from baseline to Week 84. Randomisation will be stratified by site, and participants randomised with a 1:1 allocation to sirolimus or placebo. The justification for an 88-week study is the variation at which patients with IBM change over time and the generally slow disease progression. The average change of the IBM-FRS total score over 12 months is a 3-point decline, but the standard deviation is quite large. To maximise the ability of this trial to detect a clinically and statistically significant difference between the sirolimus and placebo groups, a duration of 88 weeks was selected to balance the slowly progressive nature of the disease with the feasibility of a longer duration trial. An interim futility analysis will take place once 50% of participants have completed Week 84 (end of active study drug period).

A placebo-controlled trial design has been selected with consideration of the slowly progressive nature of IBM and the potential toxicity of the study drug. We acknowledge there is potential for unintentional unblinding of treatment allocation through manifestation of side effects of sirolimus, such as elevation of serum lipid levels and mouth ulcers. Whilst adverse events (AEs) observed by or reported to the study team may be consistent with sirolimus side effects and may therefore be considered to introduce potential bias or inadvertent unblinding, the safety of the participant has been prioritised. AE data from previously published RCTs using sirolimus vs. placebo demonstrated a similar frequency of AEs reported in both the sirolimus and placebo groups

(22), suggesting that the number of AEs observed is not likely to inadvertently unblind the study team.

Consideration has also been given to the potential for safety blood tests (other than sirolimus levels) to inadvertently unblind the study team or participants. For example, serum lipids may be elevated by Sirolimus. This risk is mitigated by the requirement to treat elevated lipids identified at screening prior to randomisation. In addition, in a prior phase III RCT Sirolimus trial in patients with lymphangioleiomyomatosis (the MILES Trial) (22), serum lipid levels did not result in significant inadvertent unblinding (personal communication McCormack). The risk of unblinding is mitigated as best as possible through robust blinding procedures embedded in the study design. Serum sirolimus levels, which would definitely unblind the study team/clinician, will be sent only to an independent, unblinded medical safety monitor in each region who directs any required dose modifications based on serum sirolimus levels. To ensure that dose adjustments are not unblinding, medical safety monitors will also adjust participants within the placebo group. Other safety blood tests may be reviewed by the local study site principal investigator (PI), who is often best placed to understand the context and significance of any changes.

Governance and oversight

This study is being conducted as an investigator-initiated, collaborative research group study. The sponsoring institution, the Perron Institute for Neurological and Translational Science, is responsible for overall governance and conduct via the Coordinating Principal Investigator (CPI). The study has a Trial Steering Committee (TSC) comprising of the CPI (MN) and two Co-Coordinating Principal Investigators, one for each of the USA (MMD) and Europe (UAB). Each region has a nominated Sponsor Representative/Legal Representative. A Data and Safety Monitoring Committee (DSMC) has been assembled to provide impartial monitoring of the study. The study is subject to all local ethical and regulatory approvals at each site.

Primary objective

To assess the efficacy of sirolimus 2mg daily compared to placebo in slowing or stabilising the progression of IBM, as measured by the mean change in patient function using the IBM-FRS total score from Baseline to Week 84.

Secondary objectives

1. To assess the safety and tolerability of sirolimus when administered to participants with IBM through comparison of the frequencies and types of adverse events in both groups.
2. To assess the efficacy of sirolimus compared to placebo in slowing or stabilising progression of IBM using the change in 6-minute walk test (6MWT) distance from baseline to Week 84.
3. To measure, as part of the 6MWT, the 2MWT, and correlate it with the 6MWT distance.
4. To assess the efficacy of sirolimus compared to placebo in slowing or stabilising progression of IBM by using the change in standardised modified Timed Up and Go (mTUG) from baseline to Week 84.
5. To assess the efficacy of sirolimus using changes in patient reported outcomes (PROs: EAT-10, SF-36, sIFA, HAQ-I and PROMIS Fatigue SF 7a) and number of falls from baseline to Week 84.
6. To assess the efficacy of sirolimus in slowing or stabilising disease progression using changes in maximal voluntary isometric strength (MVIS) in quadriceps, hand grip and pinch grip, as assessed using a hand-held dynamometer (Citec Hand-Held Dynamometer), from baseline to Week 84.
7. To assess the efficacy of sirolimus in slowing or stabilising disease progression using changes in total muscle strength via manual muscle testing (MMT) in MMT12 (International Myositis & Assessment Clinical Studies Group (IMACS) MMT8 plus an additional 4 muscle groups affected in IBM including the Flexor Pollicis Longus, wrist flexors, elbow extensors and hip flexors).
8. To compare the sensitivity to change of the IMACS MMT8 vs. the IBM-modified MMT12 from Baseline to Week 84.
9. To assess the applicability, tolerability and validity of current standard outcome measures in IBM.

Exploratory objectives

1. To examine response to treatment stratified by HLA genotype and anti-cytosolic 5'-nucleotidase 1A antibody status.
2. To compare the treatment groups with respect to changes in inflammatory markers, including cytokines, and inflammatory cells as measured by flow cytometry.

Sample size

This is an RCT testing a continuous response variable (IBM-FRS) from independent control and experimental subjects with 1 control(s) per experimental subject. The primary outcome variable in this trial is the change from baseline to Week 84 in the IBM-FRS total score. The IBM-FRS is a United States of America Food and Drug Administration (FDA) accepted outcome measure in IBM interventional therapeutic studies (23).

Prior IBM studies suggest that the annual decline in IBM-FRS is between 2.7–3.8 points (24-26). In a Muscle Study Group (MSG) report (24) based on the study of high-dose beta-interferon-1a in IBM, the mean change in IBM-FRS over 24 weeks in 30 participants was 1.357 points (SD 2.45), which assuming linearity translates to a mean 2.7-point decline over 12 months. In a longitudinal study of IBM, 23 patients showed a mean decrease in the IBM-FRS over 1 year of 3.8 points (SD 3.2) (25). In the pilot study of arimoclomol 826), the IBM-FRS scores of the 8 placebo group participants decreased by a mean of 3.50 (SD 3.35) at Month 12.

In the sirolimus pilot trial (21), the mean decline in the placebo group (n=22) was 2.91 points (SD 5.54) compared to a mean decline of 1.05 points (SD 3.63) in the sirolimus group (n=22) (Tables I and II, Appendix 1). Therefore, for the present trial we have assumed a mean rate of decline in the IBM-FRS of approximately 2.8 points per year in the placebo group and ap-

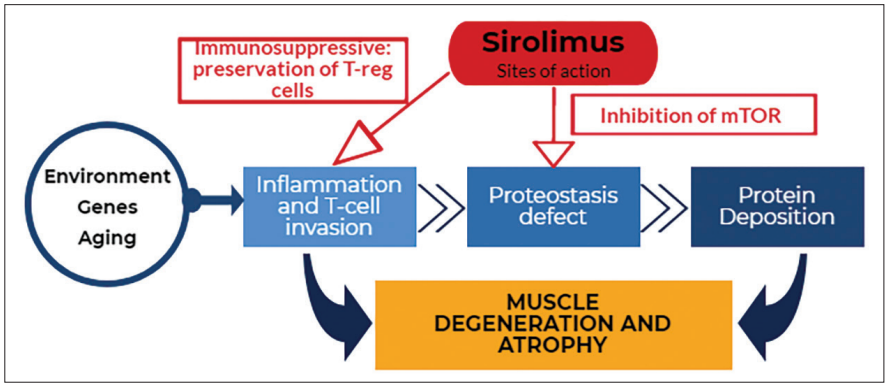

Fig. 1. Proposed pathogenesis of IBM (adapted from Britson *et al*. 2018) and potential sites of action of sirolimus in IBM.

proximately 1.0 point per year in the sirolimus group (based on the sirolimus pilot trial). Over the 84-week trial period, these declines translate to 4.67 points in the placebo group and 1.67 points in the sirolimus group. We have also assumed a conservative standard deviation of 5.5 points based on data from the sirolimus pilot trial.

With the above assumptions and, accounting for the interim analysis, a sample size of 54 participants per group (108 total) will provide 80% power to detect a treatment group difference in mean response of 3.0 points, using a two-sample t-test and a 5% significance level (two-tailed). To account for an anticipated 20% drop-out rate over 84 weeks, the sample size will be inflated to 70 participants per group (140 total).

Recruitment

Trial sites have been selected based on:

1. Expertise, interest and experience in IBM and clinical trials of the Principal Investigator and study team at each site;
2. Site's IBM cohort size; and
3. Capability and resources to run the trial at sites.

Each selected trial site is an active neuromuscular trial centre. This study will recruit 140 participants across 14 trial sites in Australia, Europe, and USA. Participants will be recruited primarily from existing patient cohorts at participating study sites, all renown for IBM patient care. Information about the study and contact details for participating sites will be disseminated to patients via study investigators and their clinical colleagues, as well as via patient advocacy groups. Patients wishing to take part who are not currently registered at a participating site may request referral by their specialist to a participating site for the purpose of consideration for inclusion in the trial. The decision to accept any such referrals will be at the discretion of the Site Principal Investigator.

Eligibility criteria (Appendix 2)

Inclusion criteria

Adults who are able to provide informed consent, aged 45 years or older, who have been diagnosed according to the European Neuromuscular Centre (ENMC) criteria 2011 (27) with IBM, who are able to walk a minimum distance of 200m and a maximum distance of 500m within 6 minutes (walking aids, including frames, may be used), with evidence of disease progression over the last 12 months, as determined by a neuromuscular specialist through patient history, physical examination, MMT, IBM-FRS or other metrics.

Key exclusion criteria

(Appendix 2 for full list)

- Inability to complete a mTUG or any other study procedure at screening;
- Unwillingness or inability to comply with study interventions or study schedule, including inability to swallow the study medication;
- Hypersensitivity to sirolimus, everolimus or any compound of the oral solution;
- Any prior exposure to sirolimus or everolimus within the last 6 months;
- Presence of any other clinically significant disease that might interfere with the patient's ability to comply with study procedures, or places the patient at greater risk for Serious Adverse Events (SAEs);
- Current use of any other immunosuppressive or immunomodulatory medication;
- Other medications or products that may significantly affect the metabolism of Sirolimus at screening (see concomitant medications below);
- Pregnancy or planning a pregnancy.

Randomisation

The results of all assessments conducted at the screening visit will be recorded in the electronic data capture (EDC) system and must be reviewed by the Site PI to confirm eligibility prior to randomising a patient to the study. If the Site PI confirms participant eligibility for the trial, the participant will undergo randomisation at the baseline visit by allocation of the next available sequentially numbered treatment kit at site. Site treatment kits will be randomised to active or placebo treatment arms at the central pharmacy using block randomisation.

Blinding and treatment allocation

All participant-facing study personnel will be blinded to treatment allocation until data collection is completed for all participants and the database is locked. The local safety medical monitors will be necessarily unblinded and fire-walled from the blinded team. The local safety medical monitors will receive sirolimus level results, which will unblind to treatment allocation and they will also hold the unblinding key from the central pharmacy. This unblinding key identifies treatment allocation by treatment kit number. However, in the event of an emergency, patients should be assumed to be on active treatment.

The DSMC are unblinded to treatment allocation as part of review of safety and efficacy data for the study.

To maintain blinding for participant-facing study personnel, the study drug and placebo will be presented in identical opaque capsules, and the packaging will also be identical for both study drug and placebo. Treatment allocation will not be discernible by differences

in taste, smell, weight or density of the capsules. The study interventions do not differ across the treatment groups, and the study manual of operations guides data collection, particularly participant-reported data, to assist with reducing risk of inadvertent unblinding and discourage speculation regarding treatment allocation.

Outcomes

The study schedule provided in Appendix 3 details the visit timepoints and activities within each study visit. Participants are asked to attend 10 study visits (+ 1 Screening Visit) over an 88-week period. A visit window of ± 14 days is considered acceptable for all scheduled study visits except for Week 4, which is restricted to ± 7 days (Visit 2) for safety reasons. Any visits occurring outside of this window must be documented by the site as a protocol deviation. Visits 5 (Week 36) and 7 (Week 64) may be performed at an authorised, delegated site (other than the study site), or as remote study visits. Physical examination by a study physician at these timepoints will only be required if clinically indicated.

The following outcomes were thoughtfully selected (28, 29) will be assessed in the order listed below: IBM-FRS, 6MWT/2MWT, MMT, MVIS, mTUG. For MVIS, quadriceps muscle strength, hand grip and pinch grip will be measured by hand-held dynamometry (HHD). All sites will be provided with a Citec hand-held dynamometer, with hand grip and pinch grip applicators, for measurement of MVIS.

Electronic Patient Reported Outcome measures (ePROs) are completed either on-line just prior to study visits, or may be completed at the study visit between the IBM-FRS and the remainder of the physical outcome measures. The ePROs included in this study are the Health Assessment Questionnaire (HAQ-1), RAND Short Form 36 (SF-36), sIBM Functional Assessment (sIFA), Eating Assessment Tool (EAT-10) and PROMIS Short Form – Fatigue 7a.

Participants will be sent a weekly study diary (survey) automatically via the EDC system (CastorEDC) via email. This diary will request information on any health or symptom changes, any medication changes and any missed doses of study drug, as well as capturing basic information regarding exercise routine. We are capturing number of falls as reported via weekly falls diary.

Safety blood samples will be obtained at each study timepoint, and any early termination visit. Participants will undergo physical examination at study visits, as described in the Schedule of Events. Adverse events will be identified via participant report, observations (*e.g.* vital signs, physical examination), urinalysis (UA) and safety blood tests.

Study treatment

The starting dose for the study will be 2 mg sirolimus (two 1 mg over-encapsulated tablets) or matched placebo daily, with dose modification as required. Serum sirolimus levels will be monitored via local unblinded medical safety monitors, who will notify site PIs of any necessary dose adjustments. The dose may be adjusted if the sirolimus levels are measured outside of therapeutic range (4–10 ng/ml). Dose adjustments will also be made in the placebo group to maintain study blind. Participants will take their first dose of study drug during their baseline (Week 0) visit.

Statistical analysis

The primary outcome variable is the change from baseline to week 84 in the total score on the IBM-FRS. The null hypothesis to be tested is that the mean value of this outcome variable is the same in the sirolimus and placebo groups. The alternative hypothesis is that the mean value differs between the groups (two-sided).

Analysis

- *Full Analysis Set (FAS):* The FAS includes all randomised patients. Patients in the FAS will contribute to the evaluation 'as randomised'.
- *Safety Set:* The Safety Set includes all patients who receive any amount of trial medication. Patients in the Safety Set will be analysed according to treatment actually received. The definition of "*actually received*" will be based on simple counting of the number of days on either of the two treatments. Further details will be provided in the Statistical Analysis Plan (SAP).

Description of statistical methods/data analysis plan

Data plan. Data will be collected in an EDC system (CastorEDC) custom-designed by the study team. Direct entry to the EDC system (electronic source data) is encouraged, with the EDC system designed to support the study visit flow. Study data entered into the EDC system are de-identified, with sites retaining the link table of participant information and study ID. Study documentation and records will be kept securely at study sites for a minimum of 15 years after the study has been completed. This includes the locked study database, which will be kept as an electronic file on local server by the Central Coordinating Team/Sponsor. Site PIs will act as custodians of archived data at their sites, with the CPI/Sponsor custodian of centralised data and the study database. Following the minimum retention period, the CPI/Sponsor will determine whether the research data should be retained and made available for future research projects, as per the approvals and consent. If it is determined that data an documents will be destroyed, the CPI/Sponsor will inform the Site PIs and agree on method of destruction.

(a) Baseline descriptive statistics

The distributions of demographic and clinical characteristics will be described for the treatment groups as well as the overall cohort using standard summary statistics.

(b) Analysis of the primary efficacy endpoint(s)

In accordance with the intention-to-treat principle, all available data from all randomised participants will be included in the primary statistical analysis. The analysis will involve the use of a repeated measures analysis of covariance model for the IBM-FRS (*i.e.* the so-called "mixed model repeated measures", or MMRM, analysis strategy (30) with terms for treatment

group (sirolimus, placebo), site, time, treatment-by-time interaction, baseline IBM-FRS score, and the treatment-by-baseline IBM-FRS score interaction.

An unstructured covariance matrix will be used to model the dependence among the within-participant observations. If the model fails to converge, alternative covariance structures will be considered instead.

The model will be used to determine the 95% confidence interval for the difference in adjusted group means between sirolimus and placebo at Week 84, along with a *p*-value to determine the statistical significance of the treatment effect. The model will yield similar information concerning treatment group differences at other time points, but these analyses will be considered to be secondary.

(c) Analysis of the secondary endpoint(s)

The statistical methods to be used to analyse the primary efficacy endpoint will also be used to analyse the secondary outcome variables for efficacy, including 6MWT distance walked (at minutes 2 and 6), strength outcomes (quantitative quadriceps strength and MMT scores (including comparing IMACS MMT8 *vs*. a proposed MMT12), grip strength, pinch strength), HAQ-I, sIFA, PROMIS Fatigue SF 7a, SF-36 scores, EAT-10, falls, and mTUG. We will perform a hierarchical analysis according to the following order: 6MWT, HAQ-1, sIBM Physical Functioning Assessment, mTUG, handgrip strength, EAT-10, PROMIS Fatigue, SF-36. This testing hierarchy order will be used if the IBM-FRS is found to be positive. Items ranked are based on clinical relevance to IBM.

(d) Additional sub-group analyses

We will investigate the interactions between treatment group and selected baseline variables including site, IBM-FRS score, 6MWT distance, site of onset, HLA genotype and CN1A antibody status. This will be done by adding the appropriate main effect and interaction terms to the primary analysis model. Since the power to detect potentially meaningful interactions will be limited, the magnitude of treatment effects in the relevant subgroups will be examined. The observation of clinically important subgroup differences in treatment effects (*e.g*. in those with low *vs*. high IBM-FRS scores at baseline) will serve as hypothesis generation for possible future studies designed to specifically address the issue of differential therapeutic response.

(e) Sensitivity analyses

The primary analyses will be performed according to the intention-to-treat principle and will include all available data from all randomised participants. The repeated measures analysis of covariance model to be used for the primary analyses uses restricted maximum likelihood to estimate the parameters of interest (treatment effects) using available data from all participants. This direct likelihood method accommodates missing data in a valid manner under the missing at random (MAR) assumption (31). Sensitivity analyses to the MAR assumption will be performed using a control-based multiple imputation approach based on pattern mixture modelling (32). Details of the multiple imputation approach will be specified in the SAP.

Safety analyses

Adverse events will be summarised by treatment group, maximum severity, and perceived relationship to study medication. Continuous measures of safety (vital signs, laboratory test results) will be presented using descriptive statistics. The SAP will include the full specification of the safety and tolerability analysis.

Adherence and retention analyses

Compliance data (capsule counts) will be summarised by treatment group, overall and by visit. Participant disposition (study completion, study completion on a reduced dosage or off study drug, withdrawal) will also be summarised by treatment group.

Planned interim analyses

The Sponsor and TSC will monitor blinded safety data on an ongoing basis and the DSMC will monitor safety and tolerability according the DSMC charter.

For this study, the DSMC comprises three members, including clinical trial and disease specialists, and a biostatistician. The DSMC is independent from the study team and sponsor.

A single interim analysis for efficacy and futility will be performed for the primary outcome variable after 50% of the participants have completed (or were scheduled to have completed, based on their randomisation date) their Week 84 evaluation and will only include data from these 50% of participants. The analysis will involve a comparison between the sirolimus and placebo groups using the statistical model described above for the primary outcome variable. The efficacy and futility boundaries will be those determined by O'Brien-Fleming α-spending and β-spending functions, respectively. In this case, the efficacy boundary will be $Z = 2.736$ and the futility boundary will be $Z = 0.697$ for the interim analysis.

Patient/consumer and public involvement

This protocol, study design and all participant-facing documents have been developed with considerable input from an Australian Myositis Research Consumer Panel. This panel is comprised of over 15 individuals with lived experience of myositis, including IBM. Members of the consumer panel contributed to refinement of the protocol and study design, in particular to review the feasibility and likely tolerability of the proposed study schedule and interventions.

Consumers also made significant contributions to the participant-facing documents, including the Participant Information and Consent Form, which includes infographics, visual aids and formatting suggested by consumers to aid readability and understanding. The inclusion of an exercise question within the weekly study diary resulted from input from consumers during their review of the protocol.

In addition to this direct consumer review, the study design included peer review from the International Myositis Assessment and Clinical Studies Group

(IMACS), as well as multiple grant reviewers including NHMRC, NIH grant reviewers, and feedback incorporated into the final study design.

Study coordination consultancy is provided by the University of Rochester, USA Data Coordinating Center of the Muscle Study Group (MSG) along with statistical support (MPM).

Ethics and dissemination

Prior to the commencement of the study at any site, the protocol, appendices and any amendment(s), participant information and consent form, and any other participant-facing items (if applicable), will be submitted for approval to the locally-accepted human ethics review board. Local governance and regulatory procedures will be followed before activation of recruitment at sites. The data management plan of the study specifies storage and use of the data generated within the study. Publication of study results is planned following study completion, as is presentation of results within academic/clinical forums as well as consumer and community forums. Following publication of the study results, applications can be made to the study team for access to the de-identified study data, and such applications will be subject to consideration of ethical approvals related to original data collection and use, as well as any proposed use. If results support changes to best practice for IBM clinical care, plans will be implemented for translation and further evaluation of any interventions.

Take home messages

- Inclusion body myositis (IBM) is an inflammatory muscle disease of ageing involving cell stress and disrupted autophagy, which currently has no effective disease-modifying therapies.
- This multicentre global phase IIb/III randomised controlled trial is to validate the findings of a prior single-centre phase II study[1] suggesting that sirolimus might slow progression of disease.
- If shown to be efficacious, sirolimus will be the first disease-modifying treatment for patients living with IBM.

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The trial sponsor is the Perron Institute, QE II Medical Centre, Perth, Western Australia, Australia. There are sponsor delegates in each country/region represented in this trial. The sponsor has no role in study design, data analysis or publication. Roles and responsibilities of the groups important in this trial oversight are outlined in Appendix 4.

Competing interests

U.A. Badrising: the LUMC receives grants for UAB from Prinses Beatrix Spierfonds and Association Française contre les myopathies as well as compensation for clinical trial activities from Fulcrum Therapeutics.

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M.M. Dimachkie serves or has recently served as a consultant for Abata/Third Rock, Abcuro, Amicus, ArgenX, Astellas, Cabaletta Bio, Catalyst, CNSA, Covance/Labcorp, CSL-Behring, Dianthus, Horizon, EMD Serono/Merck, Fortrea, Ig Society, Inc, Ipsen, Janssen, Medlink, Nuvig, Octapharma, Priovant, Sanofi Genzyme, Shire Takeda, TACT/Treat NMD, UCB Biopharma, Valenza Bio and Wolters Kluwer Health/UpToDate. He has received research grants or contracts or educational grants from Alexion/AstraZeneca, Alnylam Pharmaceuticals, Amicus, Argenx, Bristol-Myers Squibb, Catalyst, CSL-Behring, FDA/OOPD, GlaxoSmithKline, Genentech, Grifols, Mitsubishi Tanabe Pharma, MDA, NIH, Novartis, Octapharma, Orphazyme, Ra Pharma/UCB Biopharma, Sanofi Genzyme, Sarepta Therapeutics, Shire Takeda, Spark Therapeutics, and The Myositis Association.

M. Needham has provided consultancies to CSL and Abcuro, has received honoraria and is a member of the speakers' bureau of Sanofi, and has received funding from the Australian National Health and Medical Research Council.

The other authors have declared no competing interests.

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