

Design and objective of HERCULES and ATLAS: randomised, double-blind, placebo-controlled, multi-centre Phase 3 study investigating once-daily mexiletine prolonged release in myotonic dystrophy types 1 and 2

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Introduction

- Myotonic dystrophies (DM) are a heterogeneous group of hereditary, rare diseases, classified as DM1 and DM2.¹
- Myotonia is a common and defining symptom of DM1 and DM2 that results in impairment across many different domains of patients' quality of life (QoL).^{1,3}
- Current DM management relies on off-label symptomatic treatment, which may include mexiletine for myotonia:
 - Mexiletine has been used as an antimyotonic treatment for several decades;⁴
 - In randomised-controlled trials, mexiletine improved stiffness, QoL, and was well tolerated in people with non-dystrophic myotonia.^{5,6}
- While mexiletine use for DM is supported by physicians and patient groups, there is a limited evidence base, and myotonia remains undertreated in people with DM.⁴
- Therefore, regulatory approval of mexiletine in DM is needed to ensure optimal use of this drug in clinical practice.⁴
- A once-daily (QD), prolonged-release (PR) mexiletine formulation has been developed to allow for improved swallowability, tolerability, and potentially treatment compliance and effectiveness.

Objective

- HERCULES and ATLAS will generate 2-year efficacy and safety data for the mexiletine PR formulation in people with DM1 and DM2 across 5 EU countries and the UK (12 centres).

Mexiletine PR formulation

- The mexiletine PR formulation in clinical development has the potential to improve treatment adherence, tolerability, treatment satisfaction, treatment safety, and efficacy compared with the current immediate-release (IR) mexiletine capsule formulation (Table 1).

Table 1. Potential benefits of mexiletine PR

Potential challenges of mexiletine IR	Potential benefits of mexiletine PR
Some patients have difficulties adhering to therapies that require multiple daily dosing ⁷	QD dosing with mexiletine PR is likely to improve treatment adherence versus TID mexiletine IR
Approximately 30–40% patients experience GI AEs with mexiletine IR ^{8,9}	Mexiletine PR reduces the peaks of mexiletine exposure versus the IR formulation, which may reduce GI AEs
Some people with myotonia experience dysphagia ¹⁰	The powder for reconstitution mexiletine PR formulation, provided in unit dose sachets, may be easier to swallow than the mexiletine IR capsule
Mexiletine blood levels peak 1–4 h after mexiletine IR administration ¹¹	Mexiletine PR maintains mexiletine blood levels in the therapeutic range (0.5–2.0 µg/ml) over 24 h, potentially improving efficacy and tolerability

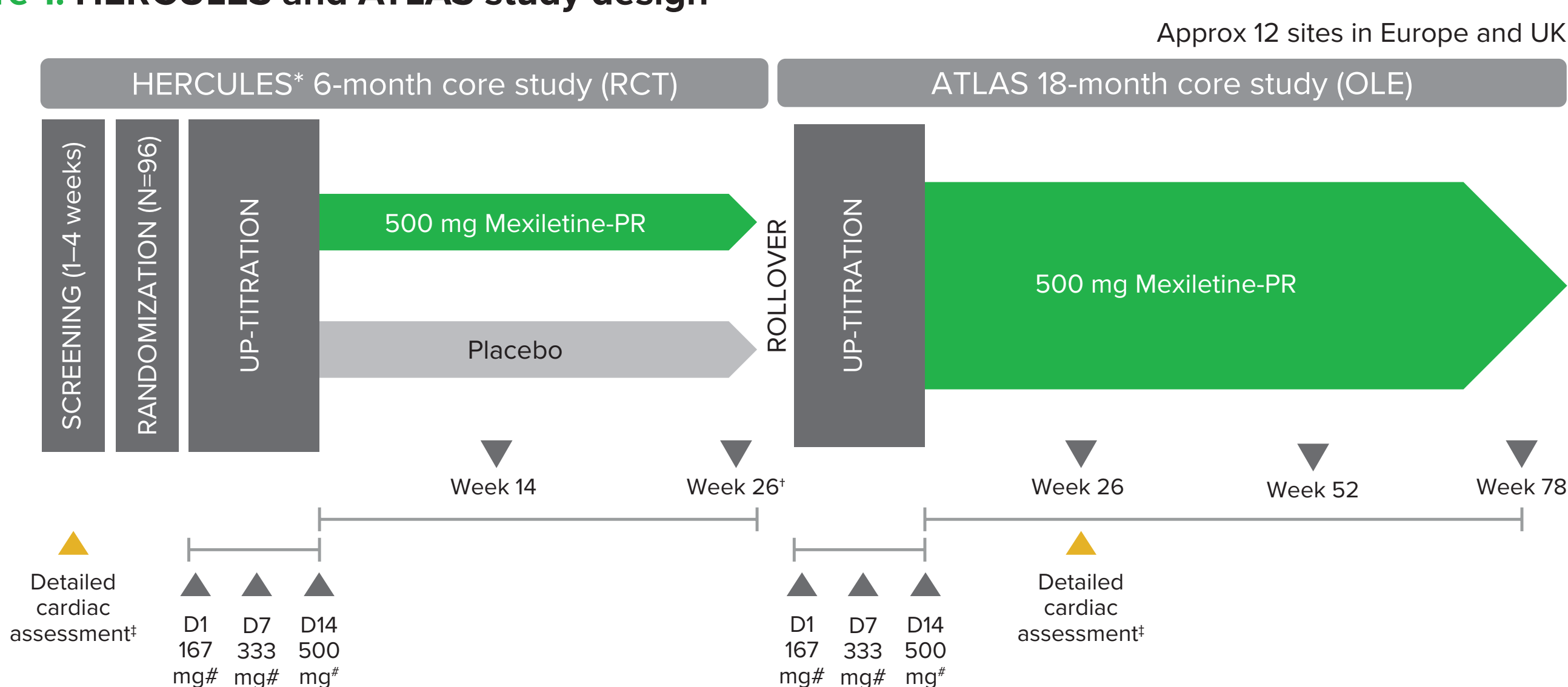
AEs, adverse events; GI, gastrointestinal; h, hour; IR, immediate release; QD, once-daily; PR, prolonged release; TID, three-times daily.

HERCULES & ATLAS

Methodology

- HERCULES will be a 6-month randomised, placebo-controlled trial (RCT); participants will be eligible to enter an 18-month open-label extension (ATLAS, Figure 1):
- Planned to include 80 participants with DM1 and 16 with DM2, with the option to re-estimate the sample size (Interim Analysis, Figure 2).
 - An interim analysis will be performed once 40 participants have completed or been subject to early termination;
 - The sample size will be adjusted from 80 up to 160 participants with DM1 based on a conditional power calculation;
 - The aim will be to achieve a conditional power of >90% for the primary endpoint, and >80% for ≥1 secondary endpoint/s.

Figure 1. HERCULES and ATLAS study design



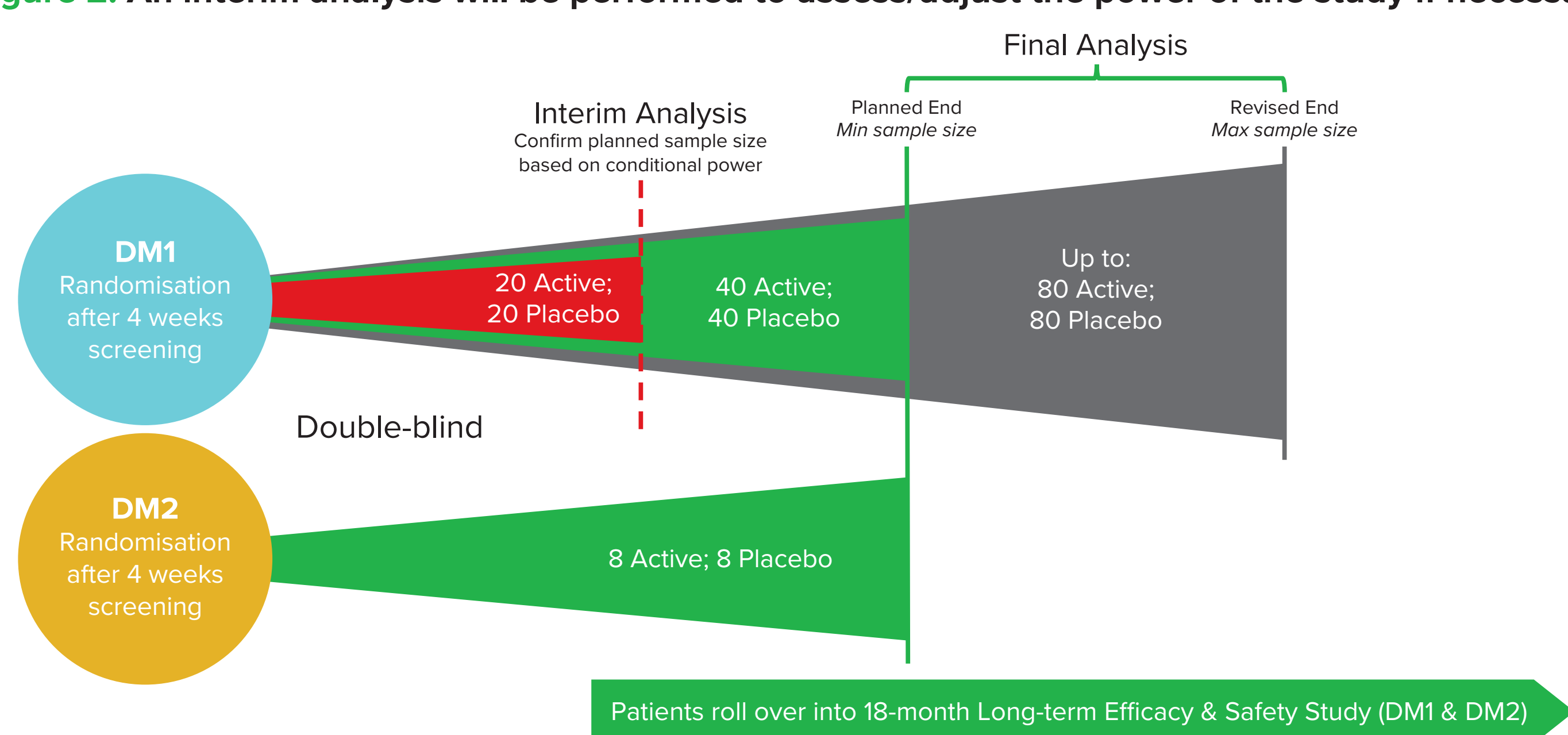
OLE, open-label extension; PR, prolonged release; RCT, randomised controlled trial.

*Includes interim analyses on 40 participants (20 enrolled per treatment group).

†Final analyses of HERCULES: *Mexiletine-PR 167, 333, and 500 mg equivalent to mexiletine hydrochloride 200, 400, and 600 mg, respectively;

‡Includes electrocardiogram and 24-h Holter.

Figure 2. An interim analysis will be performed to assess/adjust the power of the study if necessary



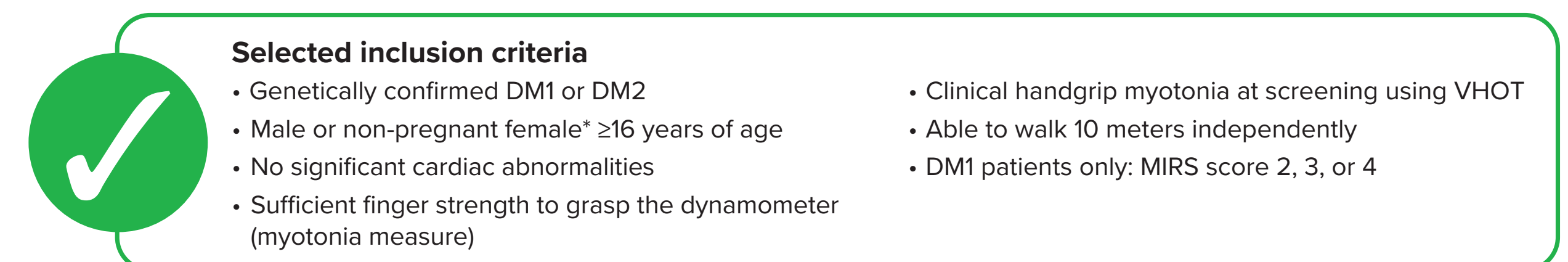
DM, myotonic dystrophy.

Conclusions

- Myotonia is a common and debilitating symptom of DM1 and DM2 that may impair many aspects of quality of life:
 - Currently there are no licensed treatments for alleviating myotonia in DM1 or DM2
- HERCULES is a new randomised clinical trial, and ATLAS is its OLE:
 - These studies will explore efficacy and safety of a new prolonged release oral liquid formulation of mexiletine.
 - Both studies will help to elucidate how symptomatic treatment of myotonia impacts QoL in people with DM1 or DM2, for up to 2 years.

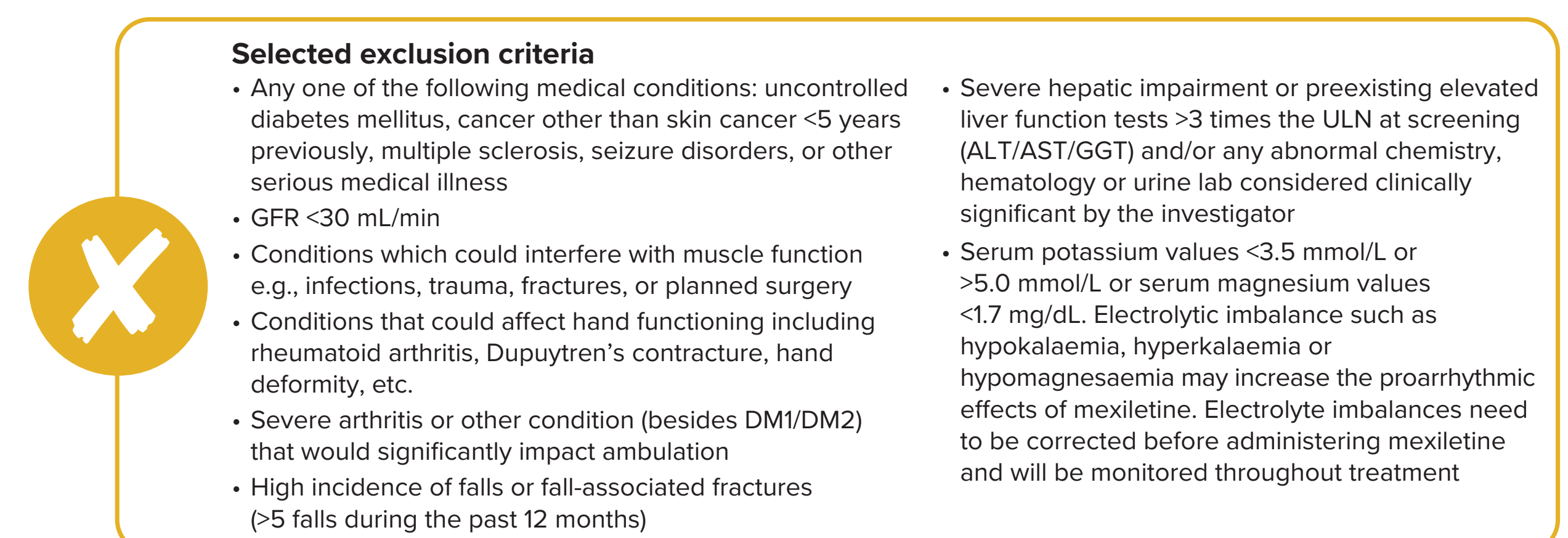
- Adolescent (≥16 years) and adult male and female participants with genetically confirmed DM1 or DM2 will be enrolled (Inclusion and Exclusion Criteria; Figures 3 and 4).
 - Participants will be randomised 1:1 to mexiletine PR or placebo.
 - Mexiletine PR will be up-titrated from 167–500 mg mexiletine PR over 2 weeks at the start of both the main RCT and extension.
- To ensure safety, detailed cardiac assessments will be performed/reviewed at screening to exclude anyone with specific risk factors, namely:
 - Resting ECG PR interval ≥240 ms or QRS duration ≥120 ms;
 - History of 3rd/2nd degree type 2 atrioventricular block or sinus node dysfunction with pauses ≥3 s, complete bundle branch block, bifascicular and trifascicular block, or any heart block susceptible to evolve to complete heart block;
 - History of sustained atrial fibrillation, flutter or tachycardia [duration >30 s]; history of non-sustained [ventricular triplets or more] or sustained ventricular tachycardia.
- Comprehensive safety assessments, including intensive monitoring of cardiac safety, will be performed throughout the study.
- Study endpoints are presented in Figure 5.

Figure 3. Key clinical inclusion criteria for HERCULES and ATLAS



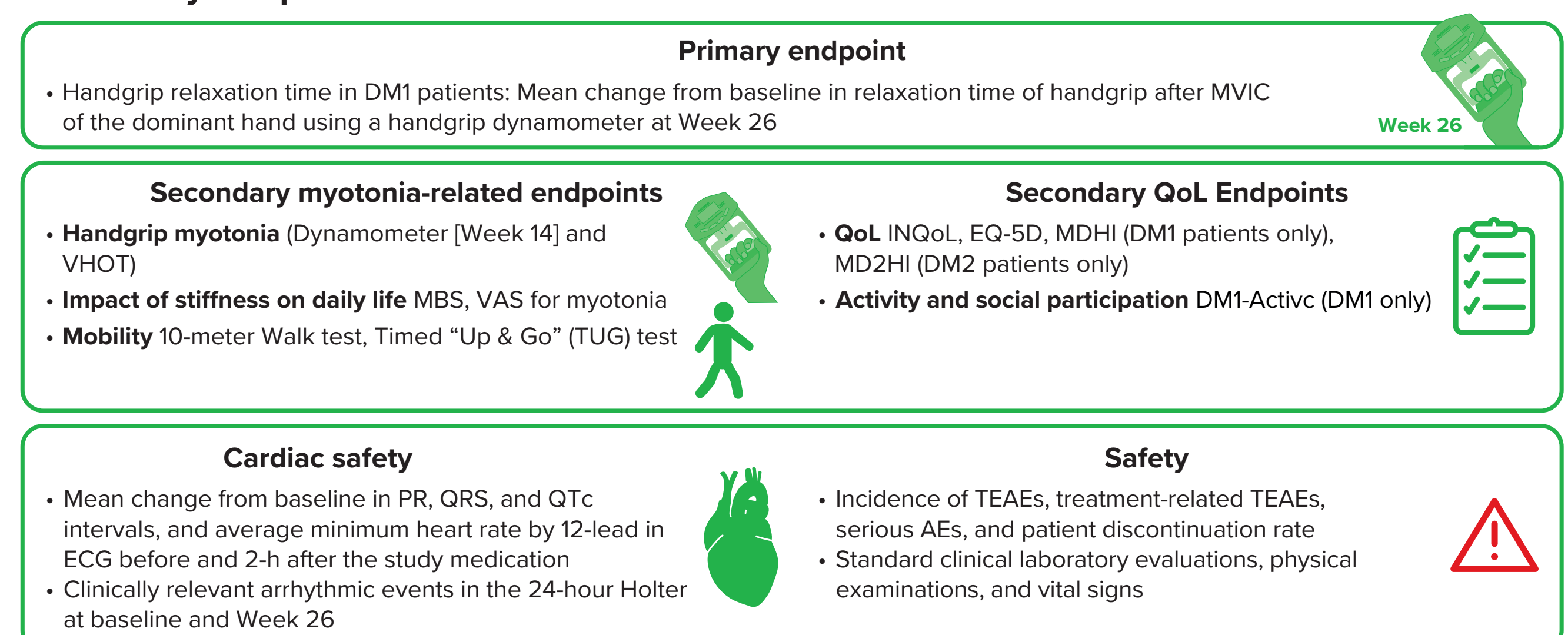
BMI, body-mass index; DM, myotonic dystrophy; ECG, electrocardiogram; MIRS, Muscular Impairment Rating Scale; VHOT, video of hand opening time. *Female participants of childbearing potential must be using highly effective birth control for the study duration and ≥7 days after last dose of study drug.

Figure 4. Key exclusion criteria for HERCULES and ATLAS



ALT, alanine transaminase; AST, aspartate transaminase; DM, myotonic dystrophy; GFR, glomerular filtration rate; GGT, gamma-glutamyl transferase; ULN, upper limit of normal.

Figure 5. Study endpoints



AE, adverse event; DM, myotonic dystrophy; ECG, electrocardiogram; INQoL, Individualized Neuromuscular QoL Questionnaire; MBS, Myotonia Behaviour Scale; MDHI, Myotonic Dystrophy Health Index; MD2HI, Myotonic Dystrophy Type 2 Health Index; TEAE, treatment-emergent adverse event; VAS, visual analogue scale; VHOT, video of hand opening time.

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