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# Design of ACHILLES Phase 3 randomised study: mexiletine PR vs. mexiletine IR in non-dystrophic myotonia

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**First randomised crossover study comparing mexiletine prolonged-release (PR) vs immediate release (IR) in NDM**

## Background/aims

- Non-dystrophic myotonia (NDM) is a rare disabling disease caused by mutations in genes coding for muscle ion channels, resulting in a delayed muscle relaxation following voluntary contraction.[1]
- NDM can severely affect quality-of-life by adversely impacting performance of daily tasks, daily life, social life and mental wellbeing.[1]
- Mexiletine is the only approved treatment for myotonia in NDM:[2]
  - Over 3000 people have received mexiletine for NDM since its approval in 2018; its safety and efficacy in NDM are supported in scientific literature and clinical practice;[3-6]
  - Mexiletine has an acceptable tolerability profile in NDM, established in clinical-trial settings; gastrointestinal (GI) effects are the most common adverse events (AEs) reported.[3-6]
- A new once daily (QD) prolonged-release (PR) formulation of mexiletine is being investigated for potential differences in adherence, tolerability and safety compared with mexiletine IR (**Table 1**).

**Table 1. The ACHILLES study aims to assess whether the modified mexiletine PR formulation is associated with measured benefits**

| Current challenges | Potential improvements associated with PR formulation |
|---|---|
| Some patients have difficulties adhering to therapies that require multiple daily dosing[7] | **QD** dosing with mexiletine PR likely to improve adherence versus **TID** mexiletine IR |
| ~30–40% patients experience GI AEs with mexiletine IR[5,8,9] | 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] | PR formulation maintains stable 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.

- ACHILLES is an exploratory, multicentre, European, open-label, crossover study assessing the safety, tolerability and effectiveness of a new QD mexiletine PR formulation versus mexiletine IR TID in patients with NDM.

## Methods

- ACHILLES is enrolling participants aged ≥16 years with genetically confirmed symptomatic NDM and evidence of handgrip myotonia (**Figures 1–3**):
  - Target study population is N=24 (n=12 mexiletine-naïve and n=12 mexiletine-experienced participants).
- Participants receive 12 weeks' treatment with mexiletine PR or mexiletine IR (mexiletine PR and IR are bioequivalent).
- After 7 days' washout, based on mexiletine pharmacokinetics to minimise carry-over effects, participants receive the opposite treatment for 12 weeks (**Figure 1**).
- Differences in administration and usability between mexiletine PR and IR formulations are key factors in treatment preference.
  - Open-label design selected to enable assessment of real-world administration, adherence and usability endpoints.

## Participants

**Figure 2. Key clinical inclusion criteria**

1. Genetically confirmed NDM
2. Male or non-pregnant females aged ≥16 years at screening
3. Body Mass Index 18.5–30 kg/m$^2$; weight ≥45 kg
4. Females of childbearing potential and males must use highly effective birth control
5. No significant cardiac abnormalities (cardiologist-determined) including electrocardiogram and echocardiogram ≤3 months before study entry
6. Myotonic symptoms severe enough to justify treatment (opinion of the study investigator)
7. Presence of clinical handgrip myotonia*

*Delayed relaxation of grip ≥ 3 seconds using a stopwatch at screening (naïve patients only) and on Day 1 (pre-dose, patients naïve and previously treated with mexiletine)

**Figure 3. Key exclusion criteria**

1. Pregnancy or lactating
2. Uncontrolled diabetes mellitus, cancer (other than skin cancer <5 years previously), multiple sclerosis, seizure disorders, or other serious medical illness
3. Glomerular filtration rate <30 mL/min
4. Medical conditions that could interfere with muscle or hand function
5. Severe arthritis/medical condition (other than NDM) that significantly impacts ambulation
6. Severe hepatic impairment or pre-existing elevated liver-function tests
7. Serum potassium values <3.5 mmol/L or >5.0 mmol/L, serum magnesium values <1.7 mg/dL or other electrolytic imbalance
8. Any other antimyotonic treatment within 4 weeks or 5 half-lives prior to baseline
9. Use of any concomitant medication that could increase cardiac risk or adverse reaction risk
10. Any cardiac safety-associated condition detected by electrocardiogram, echocardiogram and clinical evaluation

## Intervention

- Mexiletine dosing will commence at 167 mg QD, up-titrated to 333 mg in Week 1 to a maximum of 500 mg in Week 2:
  - Mexiletine PR provided as granules for oral suspension in 3 strengths (167 mg, 333 mg, 500 mg) for reconstitution in water;
  - Mexiletine IR: 167-mg hard capsule for oral administration.

## Assessments

- Safety and efficacy endpoints are shown in **Figure 4**:
  - Extensive cardiac safety testing will be conducted.
- ACHILLES is also testing the clinical myotonia rating scale (CMRS) to evaluate myotonia severity and daily impact of disability and explore the utility of CMRS as an outcome measure.

## Conclusions

- Mexiletine prolonged-release (PR) formulation has been developed with the intention of reducing the number and impact of gastro-intestinal events experienced by patients.
- It provides a QD regimen that aims to simplify mexiletine administration, thereby improving treatment experiences and quality-of-life, especially for people with dysphagia.
- The ACHILLES trial aims to compare the safety, tolerability and efficacy of mexiletine PR QD and mexiletine immediate release (IR) TID:
  - To reduce bias, ACHILLES is randomised and involves mexiletine-exposed and mexiletine-naïve participants;
  - ACHILLES is collecting objective information on adherence and tolerability in addition to patient-reported outcomes, patient preferences, and functional-capacity data.
- Enrolment in ACHILLES is expected to complete in summer 2026.

**Figure 4. ACHILLES endpoints**

**Primary endpoint**

- TEAEs, treatment-related TEAEs, SAEs, AESIs, and patient discontinuation rate between mexiletine PR and IR

**Secondary efficacy endpoints**

- VHOT
- INQoL
- MBS
- TUG test
- VAS for myotonia/stiffness
- CGI – Efficacy
- CGI – Tolerability Index

**Other efficacy endpoints**

- 10mWT
- Treatment preference
- GERDHRQoL
- Swallowing function: timed testing of swallowing
- CMRS

**Cardiac safety**

- Mean change from baseline in PR, QRS, and QTc Intervals, and average minimum heart rate by 12-lead ECG
- Standard clinical laboratory evaluations, physical examinations, and vital signs

AESI, adverse event of special interest; CGI, Clinical Global Impression; CMRS, Clinical Myotonia Rating Scale; ECG, electrocardiogram; GERDHRQoL, Gastroesophageal Reflux Disease-Health Related Quality of Life; INQol, Individualized Neuromuscular Quality of Life Questionnaire; IR, immediate release; MBS, Myotonia Behaviour Scale; PR, prolonged release; TEAE, treatment emergent adverse event; TUG, Timed "Up & Go"; VAS, Visual Analog Scale; VHOT, Video-recording of hand opening time; 10MWT, 10 metre walk test.

## Statistics

- ACHILLES is an exploratory safety study; sample size was selected based on exploratory design and feasibility considerations

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## Disclosures

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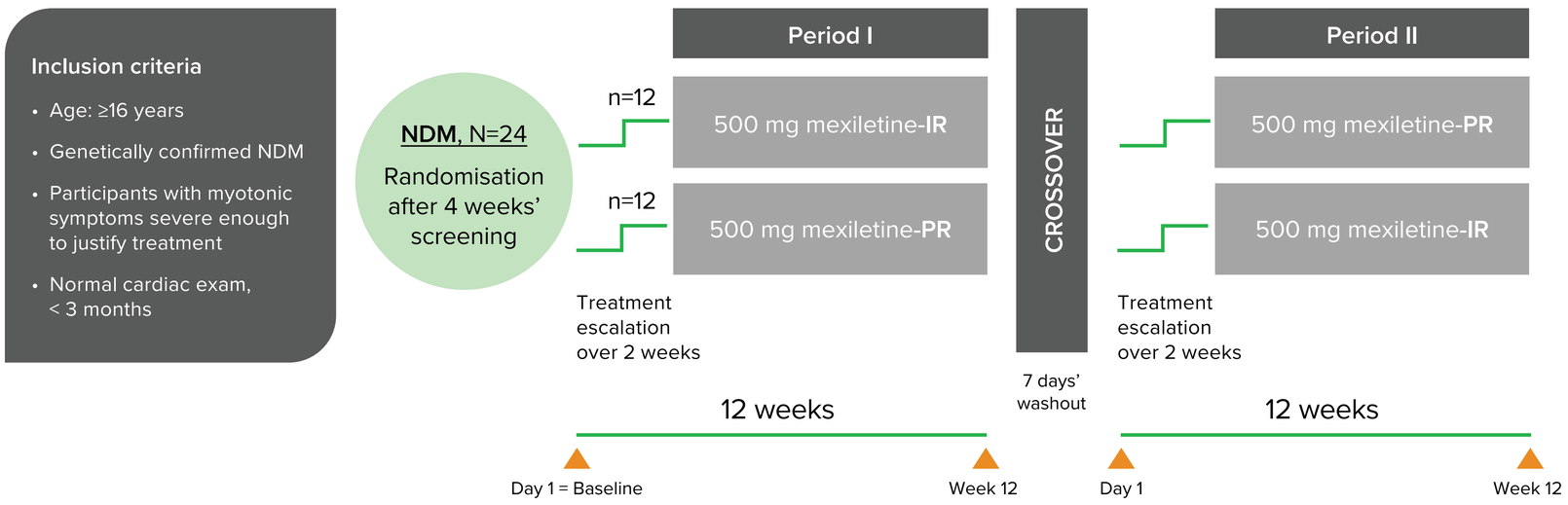
**Figure 1. Study design enables within-patient comparison**




NDM, non-dystrophic myotonia.
Mexiletine prolonged release (PR) or mexiletine immediate release (IR) started as 167 mg once-daily treatment (mexiletine 167 mg equivalent to 200 mg mexiletine HCl). Dose up-titrated at Week 1 to 333 mg and at Week 2 to a maximum of 500 mg mexiletine HCL, depending on tolerability.

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