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Portuguese consensus protocol for the initiation and monitoring of omaveloxolone in Friedreich ataxia

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Abstract

Background

Omaveloxolone is the first approved treatment for Friedreich ataxia (FRDA). Its use requires consistent patient selection, baseline assessment, laboratory, and cardiac monitoring. We aimed to develop a national consensus protocol for initiating and monitoring omaveloxolone in patients with FRDA 16 years or older.

Methods

In 2024, the Portuguese Omaveloxolone in Friedreich Ataxia (OMAF-PT) network was established after Neurology and Paediatric Neurology departments were invited to participate. Fifteen centres actively following patients with FRDA joined the network. The multidisciplinary group comprised neurologists, paediatric neurologists, residents, and cardiologists. A protocol was developed, informed by the MOXIe programme, product information, international guidelines, and clinical experience. Two email-based rounds were completed; protocol consensus was defined as approval with no unresolved substantive clinical or safety objections.

Results

The protocol addresses eligibility and treatment goals, comprehensive baseline characterization, medication interactions, neurological and functional outcomes, laboratory and cardiac surveillance, adverse-event ascertainment, adherence, and multidisciplinary care. Clinical evaluations with motor scales and patient reported outcome measures are recommended at baseline and months 3, 6, 9, and 12, and every 6 months thereafter. Telephone contacts at months 1 and 2 support early safety assessment. Liver tests, BNP/NT-proBNP, and lipids should be monitored monthly for the first 3 months and periodically thereafter, with intensified surveillance according to abnormalities and comorbidities. Structured adverse-event monitoring and annual cardiac reassessment are recommended.

Conclusions

OMAF-PT protocol translates evidence and regulatory guidance into a practical, standardised pathway to promote consistent care and data comparability while remaining subordinate to product information and individual clinical judgement.

INTRODUCTION

Friedreich ataxia (FRDA) is an autosomal recessive multisystem neurodegenerative disorder caused, in most affected individuals, by biallelic GAA repeat expansions in *FXN,* leading to transcriptional

silencing.[1, 2] Reduced levels of frataxin, the encoded protein, disrupt iron–sulphur cluster biogenesis, regulation of cellular redox pathways and haem biosynthesis.[3] The resulting impairment of mitochondrial ATP production, antioxidant defense, and iron homeostasis promotes reactive oxygen species generation and progressively contributes to cellular dysfunction and death.[4, 5] Neurological phenotype is characterised by progressive afferent and cerebellar ataxia, reflecting involvement of the dorsal root ganglia, posterior columns/ spinocerebellar pathways, and cerebellum.[2] This is typically accompanied by sensory neuropathy and pyramidal signs, which coexist with multisystem involvement, particularly hypertrophic cardiomyopathy, arrhythmias, scoliosis, diabetes mellitus, visual impairment, and sensorineural hearing loss.[1, 2] Clinical heterogeneity requires coordinated, longitudinal, multisystem care.[1, 2, 6]

Omaveloxolone is a synthetic oleanane triterpenoid shown to activate nuclear factor erythroid 2-related factor 2 (Nrf2) signalling.[7] Nrf2 regulates genes involved in antioxidant defence, iron and lipid metabolism, inflammation, and ferroptosis through binding to antioxidant response elements (AREs).[8, 9] Under basal conditions, Kelch-like ECH-associated protein 1 (KEAP1) retains Nrf2 in the cytoplasm and targets it for proteasomal degradation.[10] Oxidative stress disrupts this interaction, allowing Nrf2 to translocate to the nucleus, dimerise with small musculoaponeurotic fibrosarcoma proteins (MAF) proteins, and activate ARE-dependent gene expression.[10] In FRDA, Nrf2 nuclear translocation and downstream signalling are impaired, compromising the cellular response to oxidative stress.[11] Accordingly, pharmacological activation of Nrf2 represents a relevant therapeutic strategy targeting several pathways disrupted by frataxin deficiency.[12] The clinical development of omaveloxolone in FRDA was supported by the MOXIe programme, a multicentre phase 2 study comprising a dose-ranging first part, a randomised controlled second part, and a subsequent open-label extension.[13-16] Part 1 established the selection of 150 mg once daily for further investigation.[13] In Part 2, omaveloxolone produced a statistically significant benefit in modified Friedreich Ataxia Rating Scale (mFARS) score at 48 weeks, with a placebo-corrected difference of -2.40 points in the primary analysis population.[14] Delayed-start and propensity-matched extension analyses suggested persistence of benefit over longer-term follow-up.[15, 16] Omaveloxolone was approved for the treatment of FRDA in patients aged 16 years or older in the United States in 2023 and in the European Union in 2024.[17]

Translating evidence from clinical trials into real-world practice is inherently challenging, as trial populations may not fully represent the broader and more heterogeneous population encountered in routine care. In the MOXIe programme, participants generally had a relatively short disease duration, most remained ambulatory, and individuals with clinically significant cardiac disease or other relevant comorbidities were under-represented or excluded.[14] Consequently, the use of omaveloxolone in patients with advanced disease or substantial multisystem involvement may require additional clinical consideration. Treatment implementation may be further challenged by treatment-related laboratory abnormalities, particularly early aminotransferase elevations, as well as increases in lipid parameters and B-type natriuretic peptide (BNP).[14] Although expert recommendations support the interpretation of

aminotransferase elevations,[18] they do not encompass the full range of practical issues arising in heterogeneous real-world populations. Specialist centres therefore require a comprehensive, structured monitoring strategy that integrates regulatory safety recommendations with disease stage, comorbidities, concomitant medications, and multidisciplinary clinical judgement.

Following access to omaveloxolone in Portugal through an early access program in July 2024, clinicians caring for people with FRDA established a national network (Portuguese Omaveloxolone in Friedreich Ataxia Network – OMAF-PT). Our aim was to develop a common protocol to reduce variation between centres and support consistent clinical practice and data collection on the national OMAF-PT registry. This article describes the consensus process and presents the resulting protocol recommendations for patient assessment, treatment initiation, follow-up, safety surveillance, and management of relevant abnormalities.

METHODS

Scope and target users: The protocol applies to adolescents and adults aged 16 years or older with genetically confirmed FRDA who are being considered for, or are receiving, omaveloxolone. Its intended users are neurologists and multidisciplinary teams in Neurology centers. It addresses practical treatment initiation and surveillance and does not replace comprehensive FRDA clinical management guidelines, the European Summary of Product Characteristics (SmPC), local regulatory requirements, or individualized clinical judgement.

Consensus group and network: In 2024, the coordinating author (JD) contacted the directors of all 31 Neurology departments and three Paediatric Neurology departments in Portugal by email and invited their departments to participate in the national initiative. Two rounds of email invitations were sent. Responses were received from seventeen departments, fifteen of which were actively following patients with FRDA and subsequently joined the OMAF-PT network. Neurology residents from participating institutions and cardiologists with extensive experience in inherited cardiomyopathies were also invited to contribute. The final consensus group comprised fourteen neurologists, two paediatric neurologists, four neurology residents, and two cardiologists. Participating neurologists/ paediatric neurologists had expertise in movement disorders and hereditary ataxias, while the cardiologists provided specialist input on the assessment and surveillance of FRDA-associated cardiac disease.

Evidence identification: The coordinating author reviewed the pivotal MOXIe publications,[13, 14] delayed-start analysis,[15] propensity-matched extension analysis,[16] European product information,[17] international FRDA clinical management guidelines,[19] and subsequent publications addressing practical use and safety monitoring.[18] PubMed searches were updated to August 2026 using combinations of “Friedreich ataxia”, “omaveloxolone”, “MOXIe”, “monitoring”, “safety”, “aminotransferases”, “BNP”, “lipids”, and “drug interactions”. Reference lists of relevant publications were also reviewed. The European SmPC (version of August 2026) was treated as the primary authority for the approved indication, dosing, contraindications, warnings, interactions, and mandatory surveillance.[17]

Protocol drafting and consensus process: A first draft was prepared by the coordinating author and organized into: (1) eligibility assessment; (2) pre-treatment clinical characterization; (3) baseline evaluation; (4) concomitant medication and interaction review; (5) neurological and functional monitoring; (6) laboratory and cardiac surveillance; and (7) adverse-event management and treatment persistence. A structured electronic case report form (eCRF) was developed in parallel using REDCap,[20, 21] hosted at ULS Santo António, to standardise data collection and facilitate consistent implementation of the protocol across participating centres.

The draft underwent two rounds of review by email. In the first round, all consensus group members were invited to comment on the scientific content, clinical relevance, feasibility, and wording. The coordinating author collated the feedback, reviewed it against the available evidence and regulatory guidance, and incorporated agreed amendments. The revised protocol was circulated for a second round of review and final approval. No formal voting system or numerical agreement threshold was applied. Consensus was considered reached when the final wording received approval from the participating centres and no substantive clinical or safety-related objections remained unresolved.

Classification of recommendations: The basis of each protocol recommendation was identified, where relevant, as deriving from the European SmPC, or OMAF-PT expert practice. Statements directly reflecting regulatory contraindications, warnings, precautions, monitoring requirements, or dose recommendations were classified as SmPC-based. Additional recommendations derived from clinical experience and multidisciplinary consensus were explicitly labelled as expert practice, including thresholds for enhanced surveillance in selected patients with cardiac disease, renal impairment, anaemia, or harmful alcohol use. Within this category, some recommendations were informed by the MOXIe eligibility criteria and safety observations, whereas others were formulated by the multidisciplinary group to address clinical scenarios not adequately covered by trial evidence or regulatory guidance. No formal grading of evidence or recommendation strength was performed; accordingly, the protocol represents expert consensus rather than a guideline developed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Standard Protocol Approvals, Registrations, and Patient Consents**:** This study involved the development of expert consensus based on published evidence and professional clinical experience. It did not involve research on human participants, patient-level data, identifiable personal information, or assignment of a therapeutic intervention; therefore, ethics committee approval and informed consent were not required. The associated OMAF-PT national registry is conducted under proper ethics and data-protection approvals from all participating centres; no registry-derived patient data are reported in the present manuscript.

Data Availability: No individual participant data were generated or analysed for this consensus manuscript. The OMAF-PT protocol, monitoring schedule and case-report form template, and other materials supporting the recommendations are provided within the article and its supplementary

material. Additional non-patient materials relating to the consensus process are available from the corresponding author upon reasonable request.

RESULTS

Protocol consensus recommendations

1. Confirmation of diagnosis, indication, and treatment goals

Before treatment initiation, a molecular diagnosis of FRDA and eligibility under the current approved indication, including age 16 years or older, should be confirmed. Age at onset, disease duration, neurological phenotype, ambulatory status, relevant multisystem involvement and other medical conditions (particularly those mentioned in Table 1) should be documented to establish disease stage and support an individualised risk-benefit assessment.

Treatment goals should be agreed through shared decision-making. Discussions should address expected benefits, uncertainties in advanced disease or substantial comorbidity, monitoring requirements, reproductive considerations, and the importance of sustained adherence.

2. Identification of situations requiring non-initiation, caution, or multidisciplinary review

The current SmPC should remain the primary reference for formal contraindications, warnings, precautions, and dose recommendations. In selected clinical situations, the OMAF-PT group additionally recommends a structured multidisciplinary risk–benefit assessment (Table 1). Expert-practice recommendations are pragmatic safeguards and should not be interpreted as validated universal exclusion criteria.

3. Comprehensive baseline assessment

Before omaveloxolone initiation, a comprehensive assessment should characterize disease severity and multisystem involvement in order to distinguish pre-existing FRDA manifestations or comorbidities from findings that may emerge during treatment (Table 2 and Table 3). Clinical and genetic characterisation should be complemented by clinician-reported outcome measures (ClinROs), including the modified Friedreich Ataxia Rating Scale (mFARS) and the Scale for the Assessment and Rating of Ataxia (SARA), and patient-reported outcome measures (PROMs) as Friedreich Ataxia Activities of Daily Living (FA-ADL) and PROM-Ataxia. When resources or time constraints preclude the administration of both mFARS and SARA, mFARS should be prioritised as it was the primary efficacy endpoint in MOXIe Part 2 and could be preferred by some national regulatory authorities.[14]

In addition to the hepatic, lipid, and cardiac measures specified in the SmPC, the protocol includes broader hematological, renal, metabolic, endocrine, and targeted infectious screening. Thyroid function testing may identify subclinical hypothyroidism, whose manifestations could confound the assessment of clinical response or overlap with potential adverse events. Hemoglobin, renal function, and creatine

kinase provide context for interpreting fatigue, weakness, muscle symptoms, and subsequent laboratory changes. Hepatitis screening aims to identify previously unrecognized infection or hepatic comorbidity that could complicate interpretation of liver-test abnormalities; and HIV testing should follow clinical context and local practice. Baseline cardiovascular evaluation comprises clinical assessment, electrocardiography, echocardiography, Holter monitoring, and BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP), with cardiac magnetic resonance imaging when clinically indicated. These assessments establish a standardised reference for subsequent evaluation of treatment safety and longitudinal clinical response.

4. Revision of drug–drug interactions before treatment and at every medication change

Omaveloxolone is primarily metabolised by CYP3A4 and a weak inducer of CYP3A4, CYP2C8, and breast cancer resistance protein (BCRP). Particular attention should be paid to strong or moderate CYP3A4 inhibitors and inducers, and to clinically sensitive CYP3A4, CYP2C8, and BCRP substrates. As hormonal contraceptive exposure may be reduced, patients should be advised to use an alternative non-hormonal method or additional barrier contraception. If concomitant use of an interacting agent is unavoidable, omaveloxolone dose adjustment, or enhanced monitoring should follow the current SmPC (Supplementary Table 1).

5. Structured follow-up schedule

OMAF-PT recommends increased surveillance during the first year, particularly the first 3 months (Table 3). Telephone follow-up at months 1 and 2 allows early review of adherence, adverse events, medication changes, intercurrent illness, and laboratory results, while reducing travel burden. On-site assessments are scheduled at months 3, 6, 9, and 12, including clinical review, structured adverse-event assessment, neurological outcome measures, and laboratory monitoring. After the first year, stable patients should generally undergo clinical and laboratory assessment every 6 months and cardiac reassessment annually, with additional evaluations according to clinical need.

5.1. Neurological function

The mFARS, SARA, FA-ADL, should be administered every 3 months during the first year of treatment, and every 6 months thereafter. PROM-Ataxia frequency should be every 6 months. This schedule provides complementary clinician-rated, functional, and patient-reported measures for the longitudinal assessment of treatment response. Whenever feasible, clinician-rated assessments should be performed by the same trained evaluator, under standardised and comparable conditions. Intercurrent illness, fatigue, recent falls, or other factors that may influence performance should be documented. If such factors are present at a scheduled assessment, the evaluation should be postponed or repeated after their resolution, e.g. within 1 month, to overcome the influence of transient confounders on longitudinal interpretation.

Changes should be interpreted in relation to baseline severity, ambulatory status, individual scale domains, and the overall clinical trajectory. In non-ambulatory patients, the reduced responsiveness and potential ceiling effects of upright-stability items should be considered, with particular attention being placed to bulbar and upper-limb function, activities of daily living, and patient-reported outcomes.

5.2. Hepatic function

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin should be measured monthly during the first 3 months, and periodically thereafter (Table 3). The interruption thresholds specified in the current SmPC should be followed: omaveloxolone should be discontinued immediately if ALT or AST exceeds 5 times the upper limit of normal (ULN), or exceeds 3 times ULN with a concomitant increase in bilirubin above 2 times ULN.[17] Liver tests should be repeated promptly, and alternative causes investigated. Treatment may be reinitiated after laboratory abnormalities have resolved, with an increased monitoring frequency (e.g. every 2 weeks).[17, 18]

Aminotransferase elevations observed in clinical trials were generally asymptomatic, transient, and reversible, occurring predominantly during the first 12 weeks.[14, 17, 18, 22] Hepatology assessment should be considered for persistent, recurrent, symptomatic, mixed or cholestatic, or otherwise atypical abnormalities.

5.3 BNP/NT-proBNP and cardiac status

BNP or NT-proBNP should be measured monthly during the first 3 months, and periodically thereafter (Table 3). As cardiomyopathy is common in FRDA, changes should be interpreted relative to baseline and alongside symptoms, volume status, renal function, and cardiac imaging. An isolated elevation should not be considered diagnostic of heart failure or automatically attributed to omaveloxolone.

New cardiac symptoms, rapid weight gain, or a significant BNP or NT-proBNP increase should prompt repeat testing, cardiac evaluation, and cardiology input as appropriate. Omaveloxolone should be interrupted during the management of clinically evident fluid overload and discontinued if this cannot be adequately controlled.[17] Asymptomatic biomarker elevation without evidence of cardiac decompensation should prompt closer surveillance rather than automatic treatment interruption.

5.4. Lipids monitoring

A lipid profile, obtained under consistent conditions, should be assessed periodically (Table 3). Changes should be interpreted relative to baseline and in the context of cardiovascular risk, diabetes, nutritional status, and FRDA-associated cardiac disease. New or worsening dyslipidaemia should be addressed through lifestyle measures and lipid-lowering therapy according to standard cardiovascular guidelines and does not, in isolation, require omaveloxolone interruption.[17, 23] If a statin is indicated, potential drug interactions should inform its selection and dosing, with monitoring of clinical response, tolerability, and creatine kinase as appropriate.

5.5 Structured adverse-event ascertainment and treatment actions

At every contact, patients should be actively screened for new or worsening symptoms, irrespective of their presumed relationship to omaveloxolone (Table 4). Enquiries should cover gastrointestinal, neurological, musculoskeletal, dermatological, infectious, nutritional, and cardiac events, as well as falls and injuries. Documentation should include onset and resolution, severity, temporal and suspected causal relationship to treatment, alternative explanations, investigations performed, and outcome. Any omaveloxolone dose modification or interruption and changes to concomitant medication should be recorded systematically.

6. Promotion of adherence, continuity, and multidisciplinary care

Once-daily administration, fasting requirements, and instructions for missed doses should be reviewed regularly. Adherence may become increasingly challenging over time because of treatment fatigue, adverse events, progressive disability, or the absence of an immediately perceived benefit. Adherence should therefore be explored non-judgementally at every contact, addressing individual barriers and documenting planned or unplanned interruptions.

Care should be coordinated across Neurology, Cardiology, Primary Care, Rehabilitation, Clinical Genetics, Endocrinology, Nutrition, and other specialties according to individual needs. Omaveloxolone complements standard FRDA surveillance, rehabilitation, and symptomatic management of cardiac, endocrine, orthopaedic, swallowing, communication, hearing, and mental-health needs.

DISCUSSION

The OMAF-PT protocol provides a practical framework for translating evidence from the MOXIe program[13-15] and European regulatory requirements[17] into routine multidisciplinary care. Its central principles include comprehensive baseline characterization; early and repeated monitoring of adverse event and hepatic, lipid, and natriuretic-peptide biomarkers; systematic cardiac surveillance; proactive review of drug–drug interactions; longitudinal assessment using complementary neurological, functional, and patient-reported measures; and structured documentation of treatment-related decisions.

The protocol intentionally extends beyond the minimum monitoring requirements of the SmPC. This reflects the multisystem nature of FRDA and the need to manage patients who may be older, have longer disease duration, be non-ambulatory, or have clinically relevant cardiac and metabolic comorbidities that were excluded or under-represented in pivotal trials.[13, 14] The additional assessments are intended to establish individual reference values and improve the interpretation of subsequent findings, rather than imply that every abnormality emerging during treatment is attributable to omaveloxolone.

A further objective is to avoid overly simplistic or binary definitions of treatment response. Although MOXIe demonstrated a group-level benefit on mFARS,[14] individual trajectories are heterogeneous[24, 25] and clinical scales are affected by measurement variability and stage-dependent responsiveness.[24-28] A

one-point increase over a short interval should therefore not constitute an isolated criterion for treatment discontinuation, particularly without confirmation, contextual assessment, and consideration of the expected untreated disease course. Evaluation should integrate longitudinal neurological findings, functional status, activities of daily living, patient-reported outcomes and priorities, tolerability, adherence, and overall risk–benefit.

These recommendations represent a national expert consensus intended to support clinical practice, rather than a formal GRADE-based guideline. The strongest recommendations derive directly from the SmPC and pivotal studies, whereas several higher-risk thresholds and expanded monitoring procedures reflect pragmatic expert practice in areas where direct evidence remains limited. Explicitly identifying the basis of each recommendation enhances transparency and facilitates future revision.

The protocol should therefore be considered a living framework. Future updates should incorporate prospective real-world safety and effectiveness data, longer-term outcomes, evidence in younger patients and under-represented clinical groups, changes in product information, and the perspectives of patients and caregivers.

Strengths and limitations

The main strengths of the OMAF-PT protocol are its national, multicentre scope; involvement of clinicians with disease-specific and cardiac expertise; integration of neurological, functional, laboratory, and cardiac surveillance; and its translation into an operational schedule that can be adopted by specialist services. Limitations include the absence of a formal systematic review, evidence-grading framework, or Delphi process; and limited direct evidence in patients with advanced FRDA, clinically significant cardiac disease, or other major comorbidities. Differences in healthcare organisation and resource availability may limit transferability, particularly regarding frequent on-site assessments, Holter monitoring, and cardiac MRI. Patient and caregiver representatives were not involved in the initial process, and their participation should be prioritized in future revisions.

Implementation and updating

Centers adopting the protocol should identify a responsible clinician, use a baseline checklist, schedule laboratory tests before dispensing subsequent treatment where feasible, and establish rapid pathways for cardiology and hepatology advice. A minimum core dataset should include treatment dates, concomitant medication, mFARS, FA-ADL, key laboratory measures, cardiac investigations, and structured adverse events assessment. The protocol should be reviewed at least annually or earlier if the SmPC or major evidence changes. Local adaptation may be necessary, but mandatory regulatory safety requirements should be preserved and deviations documented.

CONCLUSION

The OMAF-PT national consensus protocol was developed both as a structured, clinically pragmatic framework for initiating and monitoring omaveloxolone in FRDA and as a common basis for systematic data collection across Portuguese centres. Its standardised assessment schedule and data-collection framework provided the foundation for a national real-world registry of patients treated with omaveloxolone, enabling prospective evaluation of treatment exposure, safety, adherence, and longitudinal clinical outcomes in Portugal. The protocol may also offer an adaptable model for other specialist centres, provided that implementation remains aligned with local resources, regulatory requirements, current product information, and emerging evidence.

Declarations

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Ethical publication guidelines statement

Consensus-development work did not involve analysis of patient-level data.

Statement of authorship

All authors contributed to the study conception and design. The first draft of the manuscript was written by Joana Damásio and all authors commented on all versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability:

No individual participant data were generated or analysed for this consensus manuscript. The OMAF-PT protocol, monitoring schedule and case-report form template, and other materials supporting the recommendations are provided within the article and its supplementary material. Additional non-patient materials relating to the consensus process are available from the corresponding author upon reasonable request.

Author Contribution

All authors contributed to the study conception and design. The first draft of the manuscript was written by Joana Damásio and all authors commented on all versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Tables 1 to 4 are available in the Supplementary Files section.

Supplementary Files

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