Synopsis d'un protocole d'étude de RIPH

(A COMPLETER POUR TOUT PROJET)

PROMOTEUR	CHU de Limoges 2 avenue Martin Luther King, 87042 Limoges Cedex
PORTEUR DE PROJET	*Pr. Philippe Couratier PU-PH* Chef de Pôle Neurosciences Tête Cou et Os Chef de Service Neurologie Coordonnateur Centre Référence Maladies rares SLA & autres maladies du neurone moteur Neurologie CHU Limoges, Hôpital Dupuytren 1 2 Avenue Martin Luther King 87000 Limoges
SENIOR SI JEUNE CHERCHEUR OU MEDECIN ACCOMPAGNANT SI PROJET PARAMEDICAL	
ACRONYME	*FG-COALS*
TITRE	*French-German cohort study to determine factors associated with weight loss in amyotrophic lateral sclerosis: pathophysiological significance and resulting therapeutic targets*
JUSTIFICATION / CONTEXTE	*Amyotrophic lateral sclerosis (ALS) is the most frequent adult onset motor neuron disease and is highly variable in terms of clinical features, genetics, and neuropathology. ALS is a fatal disease, with relentless progression within a few years after onset. A large body of evidence has demonstrated the importance of weight loss at the time of diagnosis and during disease progression (Nakayama et al., 2019; Marin et al., 2011; Desport et al., 1999). Recent studies have shown that this is a core mechanism, occurring very early before the onset of motor signs (Peter et al., 2017). Weight loss affects between one and two-thirds of patients and is adversely associated with survival (Marin et al., 2016). High caloric nutrition was able to slow weight loss and prolong survival in fast progressing ALS patients (Ludolph et al., 2020). Pathophysiological mechanisms underlying weight loss remain unknown because high-quality cohort data collecting clinical features, genetics, omics, and imaging related to the metabolic and disease status of patients are lacking.*
HYPOTHESE DE LA RECHERCHE	*We hypothesize that weight loss in ALS patients is biologically driven through specific pathways.*
OBJECTIF PRINCIPAL	*To identify clinical factors and genetic markers associated with weight loss in ALS*
CRITERE DE JUGEMENT PRINCIPAL	*Clinical factors and genetic markers independently associated with weight loss in ALS*
OBJECTIFS SECONDAIRES	*1. To identify the impact of clinical and relevant genetic variants on disease progression and survival stratified by weight loss at time of diagnosis.* *2. To identify the impact of physical activity, nutrition appetite, relevant metabolites and neurofilaments on disease progression and survival stratified by weight loss at time of diagnosis in a subset of patients (sub-cohort).* *3. To identify metabolic, inflammatory and imaging factors associated with weight loss in a subset of patients (sub-cohort).*

CRITÈRES DE JUGEMENT SECONDAIRES	*Secondary objective 1 and 2. Disease progression (ALSFRS-R slope) and survival* *Secondary objective 3. Metabolic, inflammatory and imaging factors independently associated with weight loss in ALS*
SCHÉMA DE LA RECHERCHE	*Observational, Multicenter, Cohort Study*
CRITÈRES D'INCLUSION	*- Incident cases included at the time of diagnosis with a definite, probable, probable laboratory-supported, or possible ALS according to El Escorial revised criteria (Brooks et al., 2000) and Gold Coast criteria for early diagnosis (Hannaford et al., 2021; Ludolph et al., 2015).* *- Incident ALS cases identified and followed-up in the participant ALS & Other Motor Neuron Diseases Referral Centers: seven in France and two in Germany.* *- Patients who signed the informed consent form*
CRITERES DE NON INCLUSION	*- Inability to understand the requirements of the protocol* *- Absence of treatment with Riluzole*
TYPE DE RECHERCHE **(*plusieurs choix possibles)***	☒ Etude prospective ☐ Etude rétrospective ☐ Recherche sur médicament ☐ Recherche sur dispositif médical ☐ Recherche sur produits sanguins labiles ☐ Recherche sur cosmétiques / tatouages ☐ Recherche paramédicale ☐ Rechercher sciences humaines et sociales ☐ Recherche nécessitant l'inclusion de volontaires sains / témoins ☐ Test de dépistage ☐ Test diagnostic ☒ Etude épidémiologique (descriptive ou analytique) ☐ Autre : préciser
CLASSE REGLEMENTAIRE *A PRIORI*	☐ RIPH Cat 1° ☒ RIPH Cat 2° ☐ RIPH Cat 3°
SPECIFICITE DE LA RECHERCHE	☐ Etude réalisée dans le cadre d'un parcours étudiant, thèse, mémoire : préciser et préciser la date de soutenance : ☐ Lien avec industriel / société privée
AXES DE RECHERCHE	☐ Projet entrant dans l'axe immuno-infectiologie ☐ Projet entrant dans l'axe médecine personnalisée en transplantation ☐ Projet entrant dans l'axe immuno-hématologie / oncologie ☒ Projet entrant dans l'axe neurologie ☐ Projet porté par l'équipe labellisée : préciser : ☐ Projet porté par une équipe émergente : préciser ☐ Projet faisant suite à des expérimentations faites grâce à la plateforme MICE ☐ Projet e-santé ☐ Autre :
ACTES SPECIFIQUES AU PROJET (EN PLUS DE LA PRISE EN CHARGE HABITUELLE DU PATIENT) **(*plusieurs choix possibles)***	☐ Modification de la prise en charge médicale Préciser : ☐ Modification de la prise en charge paramédicale Préciser : ☒ Ajout questionnaires, prise(s) de sang, examens médicaux ou paramédicaux

	Préciser les données recueillies : A Minimum Data Set will be exhaustively collected for all incident cases in the cohort: - Sociodemographic characteristics: Date of birth and sex - Past medical history of metabolic disorders and family history of neurodegenerative disorders - Neurological assessment: Date of first symptoms, date of diagnosis, site of onset (spinal, bulbar and respiratory), ALS phenotypes, Airlie House criteria, Gold Coast criteria, ALS-Functional Rating Scale revised (ALSFRS-R), and the King's college clinical staging. - Nutritional assessment: Usual weight (6 months before onset), body weight, height and Body Mass Index (BMI); Body weight: 12 months, 5 years and 10 years before onset - Respiratory assessment: Forced or slow vital capacity, best value of maximum inspiratory pressure and sniff nasal inspiratory pressure - Edinburgh Cognitive and Behavioral ALS Screen (ECAS) - Biological profile: Blood lipids, glucose, cholesterol and triglycerides (fasting) - Genomics: Genome-wide association study (GWAS) - Interventions: dates of gastrostomy and non-invasive ventilation - Date of tracheostomy or death A sub-cohort will be established to identify additional factors (Please see below). The following data will be collected: - Panel of causative or disease-modifying genes - Physical activity level - Nutrition and appetite scores - Metabolic profile: Fasting glucose, fasting hormonal levels: cortisol, ketone bodies - Metabolomics and lipidomics profiles - Neurofilament proteins in serum - Inflammation: T regulatory (Treg) cells proportion, macrophage transcriptome, metabolome and secretome - Imaging: MRI brain and spinal cord Peuvent-elles conduire à une modification de la PEC : Non ☐ Recueil de données issues de base de données, dossiers médicaux et/ou collections biologiques déjà existantes (et déclarées) ☐ Recherche sur transplantation / prélèvement d'organe ☐ Modification dans l'organisation de la prise en charge ☐ Autre : préciser
TRAITEMENTS/STRATEGIES/PROCEDURES DE LA RECHERCHE	*Incident ALS cases will be included across the participant centers in France and Germany. Patients will be stratified for weight loss at the time of diagnosis. A prospective follow-up every 3 months will be conducted to assess disease progression and survival. The follow-up will be of 18 months.* *A Minimum Data Set will be collected in the cohort including sociodemographic characteristics, neurological and respiratory assessment, cognition and behaviour, genetics, and biological profile. A sub-cohort will be established to identify additional factors (metabolomics, inflammation, and imaging).* *Main cohort* *- Sociodemographic characteristics will be collected at time of diagnosis* *- Genomics will be collected at time of diagnosis* *- Neurological, nutritional and respiratory assessment will be collected at time of diagnosis and every 3 months* *- Cognitive, behavior, and biological profile will be collected at time of diagnosis and every 6 months* *- During follow-up, dates of gastrostomy, non-invasive ventilation and date of death will be collected*

	Subcohort *- Physical activity level, genotype, imaging will be collected at time of diagnosis* *- Nutrition and appetite scores, metabolic and inflammation profile, metabolomics and neurofilaments will be collected at time of diagnosis and every 6 months* *- During follow-up, dates of gastrostomy, non-invasive ventilation and death will be collected*
TAILLE D'ÉTUDE	*A prospective inclusion of all incident ALS cases will be performed across the participant centers using an exhaustive approach in France and Germany (ALS & Other Motor Neuron Diseases Referral Centers).* *The number of ALS cases expected is around 600 incident cases per year in France, considering disease incidence, the population around the area of influence of the ALS Centers and the proportion of incident cases identified in these centers. In Germany, we estimate around 200 incident cases per year in the two participant centres. Overall, we expected 2400 incident cases during 36 months of inclusion and a minimal expected recruitment of 1500 patients.* *Patients will be stratified according to weight loss at time of diagnosis as follows: i) no weight loss; ii) <5% of weight loss; iii) 5-10% of weight loss; iv) >10% of weight loss. A stratified random sample procedure will be conducted to constitute a sub-cohort. Incident cases will be included in the sub-cohort for 24 months. One-quarter of incident cases identified during the inclusion period will be sampled to establish the sub-cohort (four hundred patients). A disproportionate stratified sampling will be conducted to obtain 100 incident cases for each weight loss strata.*
NOM ET COORDONNEES DU METHODOLOGISTE	*Jaime Luna MD, PhD* *Epidémiologiste* *Ingénieur de recherche* *Centre Référence Maladies rares SLA & autres maladies du neurone moteur* *Neurologie* *CHU de Limoges*
NOM ET COORDONNEES DU BIOSTATISTICIEN PRESSENTI POUR L'ANALYSE DES DONNEES	*Anaïs Labrunie, PhD* *Biostatisticienne* *Centre d'Epidémiologie, de BIostatistique et de MEthodologie de la Recherche (CEBIMER)* *Bâtiment Médico-Administratif – 1er étage - Bureau 1-80* *CHU de Limoges*
NOMBRE PREVU DE CENTRES	*ALS & Other Motor Neuron Diseases Referral Centers* *France: Seven Centers* *CHU Limoges; Hôpitaux Universitaires Pitié Salpêtrière, Paris; CHU Nice; Hôpitaux Universitaires de Marseille - AP-HM; CHU Montpellier; CHRU Tours; CHU Lille* *Germany: Two Centers* *University Clinic Ulm; MHH Hannover*
DUREE DE LA RECHERCHE	*Project implementation : 6 months* *Duration of the inclusion period: 36 months* *Duration of participation of each patient: 18 months* *Total duration of the research: 60 months*

ANALYSE STATISTIQUE DES DONNEES	*Statistical analyses will be conducted SAS V.9.3 software and the computing environment R (R Development Core Team, version 3.3.2). A p-value <0.05 will be considered statistically significant.* *Qualitative variables will be described by frequencies, percentages and 95% confidence intervals calculated using the exact method. Quantitative variables will be described using mean ± standard deviation or median and interquartile range. The comparisons will be conducted between strata related to weight loss. The comparisons of means will be performed using the ANOVA or Kruskal-Wallis test according to the conditions of application of the tests. Comparisons of percentages will use the Chi² test of Pearson or Fisher's exact test, based on conditions of application.* *Associations with weight loss will be assessed through the calculation of odds ratios with 95% confidence intervals. The outcome will be the categories of weight loss defined above. A multivariate cumulative logit regression model will be simplified using a descending step by step descending procedure. Calibration and discrimination of the final model will be assessed. Confounding will be assessed during the process and interaction will be assessed in the final model.* *Associations with progression disease will be assessed via a longitudinal model which will handle with informative missing data using a descending step by step descending procedure. The outcome will be ALSFRS-R through the follow up of the patients.* *Survival analyses will be conducted from the date of diagnosis or onset until the date of death or censoring. Kaplan-Meier method will be used. A Cox proportional hazards modeling will be performed to identify profiles associated with survival. The interaction-with-time method will be used to assess proportional hazard assumptions. The full model was simplified via a backward selection procedure considering potential confounding at each step. HRs with 95% CIs will be estimated.*
BIBLIOGRAPHIE	*- Ludolph AC, Dorst J, Dreyhaupt J, Weishaupt JH, Kassubek J, Weiland U, Meyer T, Petri S, Hermann A, Emmer A, Grosskreutz J, Grehl T, Zeller D, Boentert M, Schrank B, Prudlo J, Winkler AS, Gorbulev S, Roselli F, Schuster J,* Dupuis L; *LIPCAL-ALS Study Group (2020). Effect of High-Caloric Nutrition on Survival in Amyotrophic Lateral Sclerosis. Ann Neurol.* *- Nakayama, Y., Shimizu, T., Matsuda, C., Haraguchi, M., Hayashi, K., Bokuda, K., Nagao, M., Kawata, A., Ishikawa-Takata, K., & Isozaki, E. (2019). Body weight variation predicts disease progression after invasive ventilation in amyotrophic lateral sclerosis. Scientific Reports.* *- Peter, R. S., Rosenbohm, A., Dupuis, L., Brehme, T., Kassubek, J., Rothenbacher, D., Nagel, G., & Ludolph, A. C. (2017). Life course body mass index and risk and prognosis of amyotrophic lateral sclerosis: Results from the ALS registry Swabia. European Journal of Epidemiology.* *- Marin, B., Arcuti, S., Jesus, P., Logroscino, G., Copetti, M., Fontana, A., Nicol, M., Raymondeau, M., Desport, J. C., Preux, P. M., Couratier, P., & French register of ALS in Limousin (FRALim). (2016). Population-Based Evidence that Survival in Amyotrophic Lateral Sclerosis is Related to Weight Loss at Diagnosis. Neuro-Degenerative Diseases.* *- Marin, B., Desport, J. C., Kajeu, P., Jesus, P., Nicolaud, B., Nicol, M., Preux, P. M., & Couratier, P. (2011). Alteration of nutritional status at diagnosis is a prognostic factor for survival of amyotrophic lateral sclerosis patients. Journal of Neurology, Neurosurgery, and Psychiatry,* *- Desport JC, Preux PM, Truong TC, Vallat JM, Sautereau D, Couratier P. (1999). Nutritional status is a prognostic factor for survival in ALS patients. Neurology*

RETOMBEES ATTENDUES	*This ambitious French-German cohort proposal will allow the identification of markers that could potentially be used to personalized dietary counseling and prevent weight loss with a positive impact on disease progression and survival. The analysis of multidimensional biological factors would also provide new pathophysiological insights into the different mechanisms involved in ALS nutritional status. Advances in deciphering these factors could ensure effective nutritional therapeutic targets.* *The establishment of the French-German consortium for ALS research will create a strong network among health care centres and laboratory research teams aiming for further multidisciplinary studies on ALS.*
EVALUATION BUDGETAIRE	☐ Non réalisée ☐ Non réalisée mais des postes de dépenses déjà identifiés ☐ Réalisée (à joindre)
FINANCEMENT ***(plusieurs choix possibles)***	☐ Pas de financement nécessaire ☐ Source de financement non identifiée, à déterminer ☐ Source de financement souhaité (préciser) : ☐ AAP national : *préciser* ☐ AAP interrégional : *préciser* ☐ Soutien local : ☐ Autre AAP : *préciser* ☐ Financement industriel : *préciser* ☐ Autre source : *préciser* ☒ Financement acquis : ANR - Appel à manifestations d'intérêt accélérer la recherche et l'innovation sur les maladies rares grâce aux bases de données
VALORISATION ATTENDUE ***(plusieurs choix possibles)***	☐ Modification des pratiques ☒ Congrès ☐ Brevet ☒ Publications (ex de journaux visés) : peer reviewed academic journals ☐ Extension AMM – autorités (ANSM, commission transparence etc…) ☐ Partenariat industriel ☐ Autre :
ELEMENTS DE FAISABILITE	*Pr Philippe Couratier is the national coordinator of the French ALS Health Consortium "Filière de santé Sclérose Latérale Amyotrophique et autres maladies rares du Neurone moteur (FilSLAN)", member of the Consortium for the European Research on Epidemiology of ALS, TRICALS and the French Network on FTD/ALS.* *The ALS Research Team, coordinated by Pr. Couratier, has contributed to improving the understanding of nutrition in ALS: i) alterations in nutritional status impact survival (Desport et al., 1999, 2000). ii) weight loss at the time of diagnosis impacts survival (Marin et al., 2011, 2016b). iii) 50% to 60% of patients with ALS exhibit hypermetabolism statistically significant compared to a control population (Fayemendy et al., 2021). iv) hypermetabolism modifies the body composition at diagnosis and patients with hypermetabolism >20% have a worse prognosis than those without hypermetabolism (Jésus et al., 2018). v) creation of a specific resting energy expenditure formula for ALS patients using body composition and impedancemetry (Jésus et al., 2019, 2020). They have also conducted a randomized clinical trial to assess the benefits of early oral nutritional supplementation on neurological functional status in ALS patients (NUTRALS, ClinicalTrials.gov Identifier: NCT02152449).* *The German network for motoneuron diseases, led by Pr. Albert Ludoplh, is one of the most prestigious ALS research teams in Europe. They have successfully implemented a large clinical database with biobank using validated standardized operational procedures. The Germany participant hospital centers in the FG-COALS project have conducted a placebo-controlled multi-center study targeting weight loss in ALS (LIPCAL-ALS) using a high-calorie, high-fat nutritional supplement that yielded extremely promising results (Ludolph et al., 2020). Therefore, based on this expertise yields promising starting conditions for this project.*

PUBLICATIONS ANTERIEURES DE L'EQUIPE	*Pr. Couratier* *Total de publications : 220* *Total number of citations: 8259* *H index: 49* ***Last publications*** *- **Luna J, Couratier P**, Lahmadi S, Lautrette G, Fontana A, Tortelli R, et al. Comparison of the ability of the King's and MiToS staging systems to predict disease progression and survival in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Front Degener. 2021* *- **Couratier P**, Lautrette G, **Luna J**, Corcia P. Phenotypic variability in amyotrophic lateral sclerosis. Rev Neurol (Paris). 2021.* *- Fayemendy P, Marin B, Labrunie A, Boirie Y, Walrand S, Achamrah N, Coëffier M, **Preux PM**, Lautrette G, Desport JC, **Couratier P**, Jésus P. Hypermetabolism is a reality in amyotrophic lateral sclerosis compared to healthy subjects. J Neurol Sci. 2021* *- Corcia P, Beltran S, Bakkouche SE, **Couratier P**. Therapeutic news in ALS. Rev Neurol (Paris). 2021* *- **Luna J**, Jost J, Diagana M, Ait Aissa L, Tazir M, Ali Pacha L, et al. Clinical management and disease-modifying treatment for amyotrophic lateral sclerosis in African hospital centers: the TROPALS study. Amyotroph Lateral Scler Front Degener. 2021.* *- Fontana A, Marin B, **Luna J**, Beghi E, Logroscino G, Boumédiene F, et al. Time-trend evolution and determinants of sex ratio in Amyotrophic Lateral Sclerosis: a dose-response meta-analysis. J Neurol. 2021.* *- Corcia P, **Couratier P**, Vourc'h P. The future of ALS might move towards Genetic Therapy. Rev Neurol (Paris). 2021* *- Erazo D, **Luna J**, **Preux P-M**, Boumediene F, **Couratier P**. Epidemiological and genetic features of amyotrophic lateral sclerosis in Latin America and the Caribbean: a systematic review. Amyotroph Lateral Scler Front Degener. 2021* *- Jésus P, Fayemendy P, Marin B, Nicol M, Sourisseau H, Boirie Y, Walrand S, Achamrah N, Coëffier M, **Preux PM**, Lautrette G, **Couratier P**, Desport JC. Increased resting energy expenditure compared with predictive theoretical equations in amyotrophic lateral sclerosis. Nutrition. 2020* *- Baldin E, **Preux PM**, **Couratier P**, Pugliatti M, Marin B; FRALIM CONSORTIUM. Validity of death certificates in the identification of cases of amyotrophic lateral sclerosis (ALS) in the Limousin region, France. A population-based study. Amyotroph Lateral Scler Frontotemporal Degener. 2020* *- Vergonjeanne M, Fayemendy P, Marin B, Penoty M, Lautrette G, Sourisseau H, **Preux PM**, Desport JC, **Couratier P**, Jésus P. Predictive factors for gastrostomy at time of diagnosis and impact on survival in patients with amyotrophic lateral sclerosis. Clin Nutr. 2020* *- **Luna J**, Diagana M, Ait Aissa L, Tazir M, Ali Pacha L, Kacem I, et al. Clinical features and prognosis of amyotrophic lateral sclerosis in Africa: the TROPALS study. J Neurol Neurosurg Psychiatry. 2019* *- **Luna J, Preux PM**, Logroscino G, Erazo D, Del Brutto OH, Boumediene F, **Couratier P**, Marin B. Amyotrophic lateral sclerosis mortality rates among ethnic groups in a predominant admixed population in Latin America: a population-based study in Ecuador. Amyotroph Lateral Scler Frontotemporal Degener. 2019* *- **Luna J**, Leleu J-P, **Preux P-M**, Corcia P, **Couratier P**, Marin B, et al. Residential exposure to ultra high frequency electromagnetic fields emitted by Global System for Mobile (GSM) antennas and amyotrophic lateral sclerosis incidence: A geo-epidemiological population-based study. Environ Res. 2019*
PROJETS ANTERIEUREMENT MENES	*Pr Philippe Couratier has vast experience organizing and participating in several ALS research projects. During his career, he has received funding for research projects by multiple institutions including ANR (BMAALS program), DGOS (EURECALS program, Nutrals program), Association Française de Recherche sur la SLA (Biostaging), and Région Nouvelle-Aquitaine (ALS France-Ecuador).*