Protocol

Full Study Protocol

TRACKING NUMBER:

TITLE: Clinical characteristics, natural history, health care measures, and the frequency of genetic variants in the genes of SOD1, C9orf72, FUS and TARDBP in patients with sporadic and familial amyotrophic lateral sclerosis (ALS)

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INVESTIGATOR INFORMATION

This study is a collaboration of the Ambulanzpartner Soziotechnologie APST GmbH (Sponsor) and the Charité – Universitätsmedizin Berlin, Center for ALS and other motor neuron disorders (principal investigator).

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Protocol signature page
The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Sponsor

Date

Prof. Dr. Christoph Münch

Principal Investigator

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Prof. Dr. Thomas Meyer

Abbreviations

ALS	Amyotrophic Lateral Sclerosis
ALS-FRS	ALS Functional Rating Scale
APST	Ambulanzpartner Soziotechnologie
DSGVO	Datenschutzgrundverordnung (engl.: General data protection regulation)
fALS	Familial Amyotrophic Lateral Sclerosis
FTD	Frontotemporal Dementia
GDPR	General Data Protection Regulation
GenDG	Genetic Diagnostics Act (Gendiagnostikgesetz)
IEC	Independent Ethics Committee
MYMOP	Measure your Medical Outcome Profile
ODP	Order Data Processing
PEG	Percutaneous endoscopic gastrostomy
PI	Principal Investigator
sALS	Sporadic Amyotrophic Lateral Sclerosis
SMD	Standard Mean Difference

Study Synopsis

Tracking Number:

Protocol Title: Clinical characteristics, natural history, health care measures, and the frequency of genetic variants in the genes of SOD1, C9orf72, FUS and TARDBP in patients with sporadic and familial amyotrophic lateral sclerosis (ALS)

Version Number: 2.6

Study indication: Amyotrophic Lateral Sclerosis (ALS)

Study rationale: There is only limited data available on the frequency of genetic variants in patients with sporadic ALS (sALS) and familial ALS (fALS). In patients with sALS (patients without family history of ALS), genetic investigations do not belong to the standard of care. As a result, the patient's mutation status is commonly unknown. Even in patients with fALS (with known family history of ALS), screening for genetic mutations is not performed on a regular basis, due to lacking treatment options in the field of gene therapy. However, this paradigm is about to be changing as clinical trials on genetic medicines are ongoing and might result in the approval of new genetically investigated drugs in the future. This project is intended to investigate a large cohort of ALS patients on family history, clinical characteristics, health care measures and genetic variants in SOD1, C9orf72, FUS and TARDBP – the most commonly mutated genes in ALS. This cohort study will allow to determine the frequency of gene mutations in ALS patients in a real-world setting of ALS centers in Germany. Furthermore, the project shall enhance insights into potential differences between genetically defined cohorts by means of the course of disease and the provision of health care measures. The investigation of genetically distinct ALS cohorts is particularly relevant, as an improved understanding of the relationship between the genotype and the journey of disease is scientifically indispensable, in order to determine the therapeutic potential of future genetic therapies.

Objectives and Endpoints:

<u>Primary objective</u>

- To identify the frequency of genetic variants in the genes of SOD1, C9orf72, FUS and TARDBP in patients with sALS and fALS

<u>Secondary objectives</u>

- To investigate the demographic and social characteristics
- To investigate the family history for ALS or FTD
- To investigate the clinical classification, functional deficits and progression

- To register interventions and health care measures including percutaneous endoscopic gastrostomy (PEG), ventilation therapy,
- To register the provision with assistive technology devices, symptomatic pharmacotherapy and physical, occupational and speech therapy
- To investigate the clinical classification, functional deficits, disease progression and health care measures in a subset of ALS patients with pathogenic variants in the genes of SOD1 or C9orf72 as compared to ALS patients with no ALS-associated mutations in the investigated genes
- To register the values of serum concentration of neurofilament light chain (sNfL)
- To identify patient´s treatment expectations towards ALS therapy using the Measure Your Medical Outcome Profile (MYMOP2)

Endpoints

Primary endpoint

- Genetic variants in the genes of SOD1, C9orf72, FUS and TARDBP

Additional endpoints

- The following additional endpoints will be explored:

Family history of ALS and FTD

- Family members living with ALS or FTD
- Family members who have died from ALS or FTD

Clinical classification, functional deficits and progression

- ALS subtypes (classic ALS, progressive muscular atrophy (PMA) and primary lateral sclerosis (PLS)
- Topic of the initial symptoms
- ALS Functional Rating Scale (ALS-FRS)
- ALS progression (ALS-FRS per months)
- King's classification of clinical stages of ALS
- Serum neurofilament light chain (sNfL)

Interventions and health care measures

- Percutaneous endoscopic gastrostomy (PEG)
- Non-invasive ventilation
- Tracheostomy
- Provision with assistive technology devices
- Symptomatic pharmacotherapy
- Physical, occupational and speech therapy

Patient´s expectations towards ALS therapy

- Measure Your Medical Outcome Profile (MYMOP2)

	This evaluation is exploratory. There is no formal hypothesis that is tested.
Study design:	This study is a prospective, non-interventional registry study (analytical observational study) in an inter-cohort comparison at 18 study centers in Germany.
Study location:	18 study sites in Germany
Number of subjects:	Approximately 2,000 subjects
Study period:	The study period is about two years (August 2021 until December 2024)
Study population:	This study will be conducted in subjects aged at least 18 years, inclusive, with a diagnosis of sporadic or familial ALS.
Assessment Schedule	Study subjects will have up to 3 assessments over a period of approximately 1 year.
Key study assessments:	*Genetic variants in four ALS-associated genes* • SOD1 gene • C9orf72 gene • FUS gene • TARDBP gene *Family history for ALS or FTD* • Family members living with ALS or FTD • Family members who have died from ALS or FTD *Clinical classification, functional deficits, and progression* • ALS subtypes (classic ALS, progressive muscular atrophy (PMA) and primary lateral sclerosis (PLS) • Topic of the initial symptoms • ALS Functional Rating Scale (ALS-FRS) • ALS progression (ALS-FRS per months) • King's classification of clinical stages of ALS • Serum neurofilament light chain (sNfL) *Interventions and health care measures* • Percutaneous endoscopic gastrostomy (PEG) • Non-invasive ventilation • Tracheostomy • Provision with assistive technology devices • Symptomatic pharmacotherapy • Physical, occupational and speech therapy *Patient´s expectations towards ALS therapy* • Measure Your Medical Outcome Profile (MYMOP2)

Statistical methods:	The standardized mean difference (SMD) will be applied in this study. The SMD of each measure over up to 12 months will be estimated using the change in measure between each subject's assessments. The standardized mean difference expresses the size of intervention effect.
Sample size determination:	Due to this partly exploratory background of study project, a sample size justification is not applicable. The sample size is based on the feasibility of eligible patients to be enrolled at this site and is not based on power calculation.
Interim analysis:	An interim analysis may be performed.
Study stopping rules:	Not applicable for an observational study.

1. Visit schedule

Table 1: Visit schedule

Visit schedule	V1 M1-M3 (Baseline)	V2 M4-M8* (Follow-Up)	V3 M9-M14 (Closure)
Demographic data			
Age	x		
Gender	x		
Place of residence	x		
Social characteristics			
Employment status	x		
Marital status	x		
Education level	x		
Living arrangement	x		
Disease history			
Date of disease onset	x		
Date of initial diagnosis	x		
Age at disease onset	x		
Duration of disease	x		
Date of death (if applicable)			
Family history			
Family members who are living with ALS	x		
Family members who died of ALS	x		
Family members who are living with FTD	x		
Family members who died of FTD	x		
Family members who are suffering from neurological/psychiatric disorder	x		
Family members who died of any neurological/psychiatric disorder	x		
Clinical classification			
ALS subtypes	x		
Region of onset	x		
Functional deficits and progression			
ALS Functional Rating Sale (ALS-FRS)	x	x(2)	x
ALS progression rate (loss of ALS-FRS per month)	x	x(2)	x
King's classification of clinical stages of ALS	x		x
Serum neurofilament light chain (sNfL)	x	x(2)	X(2)
Interventions and health care measures			
Use of PEG	x		x
Use of non-invasive ventilation	x		x

Use of tracheotomy	x		x
Provision of a manual wheelchair (1)	x		
Provision of complex power wheelchair (1)	x		
Provision of a communication device (1)	x		
Provision of assistive technology (1)	x		
Physical, occupational and speech therapy (1)	x		
Riluzol and symptomatic pharmacotherapy (1)	x		
Treatment expectation			
MYMOP2, measure yourself outcome profile	x	x(2)	x(2)
Molecular genetic analysis			
C9orf72	x		
FUS	x		
SOD1	x		
TARDP	x		

M: month, V: visit; 1 = subgroup of users of APST management platform, 2 = in subgroup of patients with SOD1 mutation data will be collected more frequently (up to monthly collection of existing data of sNfL; up to weekly self-assessment of ALS-FRS using the ALS-App in addition to on-site assessment of ALSFRS-R during site visits). In the main cohort of non-SOD1 patients the collection of sNfL data is limited to the visits V1 (baseline) and V2 (follow-up).

2. Introduction

2.1. Background

ALS is an adult-onset degenerative motor neuron disorder leading to progressive motor deficits and eventually to death within a few years (Brown et al. 2017). Currently, there is no effective disease modifying drug available. A distinction is made between sporadic and familial ALS (Kiernan et al. 2021). Sporadic ALS (sALS) refers to the occurrence of ALS in a single individual without known family history of ALS or frontotemporal dementia (FTD). Reportedly, population genetic studies in ALS found sALS in more than 90% of all ALS patients (Brenner et al. 2019, Kim et al. 2020, Volk et al. 2017, Zou et al. 2017). The term "familial ALS" (fALS) relates to the occurrence of ALS or FTD in several family members of a given trait. The definition of fALS encompasses positive cases of FTD as this neurodegenerative disorder may share com–mon pathogenic pathways with ALS.

In patients with sALS, genetic tests for SOD1, C9orf72, TARDBP or other genes are not subject to standard care. The previous findings on the frequency of genetic variants in ALS-associated genes can be traced back to a few populations genetic studies of ALS (Volk et al., 2018). As a result, sALS patients and treating neurologists are commonly unaware of the patient's mutation status. Even in patients with positive or uncertain family history of ALS or FTD, screening for genetic mutations is not performed on a regular basis. Reportedly, ALS-associated genetic variants are mostly found in the genes of SOD1, C9orf72, FUS, and TARDP (Brenner et al. 2019, Kim et al. 2020, Volk et al. 2017, Zou et al. 2017). More specifically, mutations in SOD1 were found in 14.8% of patients with fALS and 1.2% of the sALS population. The disease is causing repeat expansions of the C9orf72 gene, among which 6.5% are identified of the total ALS cohort (34% of fALS, 5% of sALS) (Zou et al. 2017).

Most of the data on the prevalence of genetic variants in ALS genes are derived from European studies and deduced to the German ALS population. Furthermore, previous studies where confined – or focused – on families with fALS, whereas the frequency of gene mutations in sALS has not been systematically investigated. In the result, the actual frequency of gene mutations in ALS, particularly in sALS, is basically unknown. It is well conceivable that the frequency of SOD1, C9orf72, FUS, and TARDP might be underestimated. Moreover, fALS may be more frequent than expected as family history is not always obtained by scrutiny leading to an uncertain number of fALS patients being undetected. Given the few systematic data on genetic variants in fALS and sALS, little is known about the clinical, prognostic and interventional characteristics genetically defined cohorts in ALS.

2.2. Study rationale

There is only limited data available on the frequency of genetic variants in patients with ALS. In patients with sALS, genetic testing is not subject of standard of care. As a result, the patient's mutation status is commonly unknown. Even in patients with fALS, screening for genetic mutations is not performed on a regular basis, as there are no genetically defined treatment options available. However, this paradigm is about to be changing as controlled clinical trials on genetic medicines are ongoing which might be approved in the future (Kiernan et al. 2021, Miller al et. 2021, Hardiman et al. 2020). This project is intended to investigate a large cohort of ALS patients on family history, clinical characteristics, health care measures and genetic variants in SOD1, C9orf72, FUS and TARDBP. This cohort study will allow to determine the frequency of gene mutations in ALS patients in a real-world setting of ALS centers in Germany. Furthermore, the project shall enhance insights into potential differences between genetically defined cohorts by means of the course of disease and the provision of health care measures. The investigation of genetically distinct ALS cohorts is particularly relevant, as an improved under-

standing of the relationship between the genotype and the journey of disease is scientifically indispensable, in order to determine the therapeutic potential of future genetic therapies.

2.3. Own previous work

2.3.1 ALS center at the Charité – Universitätsmedizin Berlin (principal investigator)

The ALS center at the Charité was founded in 2002 by the principal investigator (PI) and evolved to a multidisciplinary care center serving more than 700 ALS patients. A major emphasis of the PI and his team has been the contribution to industry-sponsored and investigator-initiated trials. Prototyping, service engineering and implementation of digital and web-based solutions for managed care in ALS and other complex neurological disorders, such as Spinal Muscular Atrophy (SMA) has been realized since 2010. A current emphasis is on outcome research by means of biomarkers (large-scale investigation on neurofilament light-chain), patient reported outcomes (on innovative drugs, assistive technology devices), digital outcome markers (including sensory recognition of voice and facial expression in ALS) and clinical research with a main focus on medicines, ventilation intervention, robotic assistive systems in ALS (Meyer et al. 2018, 2019, 2020, Spittel et al. 2020).

2.3.2 APST (Sponsor)

APST was founded in 2010, being a spin-off of the ALS Center at the Charité. The digital platform “Ambulanzpartner” is the main product of APST. It serves as a digital case management and research platform with a main focus on ALS, SMA and other related disorders (Fürstenau et al, in press). The APST platform is used in more than 20 specialized care centers in Germany, serving as a digital demand platform and case management architecture connecting patients, neurological centers and health care providers. Since March 2011, more than 6.000 ALS patients and +200 subjects with adult 5q-SMA have been registered. More than 300.000 provisions of assistive devices, medicines and nutrition products have been managed at this platform. Beyond case management, the platform is being used for clinical research (Meyer et al. 2018, 2019, 2020; Holm et al. 2013), systematic analysis of health care provision (Funke et al. 2015; Funke et al. 2018) and digital assessment of patient reported outcomes, such as online capture of ALS functional rating scale (Maier et al. 2012). At the platform, the infrastructure for online assessment, in terms of legal framework, technology, usability and long-term experience, has been established. With the use of APST, a bi-directional digital communication with patients and the online assessment of questionnaires, scores and scales are facilitated. Thus, the ALS-FRS will be obtained during this study, by means of the “ALS App” smart phone application, which has been implemented recently.

3. Objectives and endpoints

3.1. Objectives

3.2. Primary objective

- To identify the frequency of genetic variants in the genes of SOD1, C9orf72, FUS and TARDBP in patients with sALS and fALS

3.3. Additional objectives

<u>The additional objectives of this study are as follows:</u>

- To investigate the demographic and social characteristics
- To investigate the family history for ALS or FTD
- To investigate the clinical classification, functional deficits, disease progression and health care measures in a subset of ALS patients with pathogenic variants in the genes of SOD1

or C9orf72 as compared to ALS patients with no ALS-associated mutations in the investigated genes
- To register available data on serum concentration of neurofilament light chain (sNfL)
- To register the history of interventions and health care measures including percutaneous endoscopic gastrostomy (PEG) and ventilation therapy
- To register the provision with assistive technology devices, symptomatic pharmacotherapy and physical, occupational and speed therapy
- To identify patient´s treatment expectations towards ALS therapy using the Measure Your Medical Outcome Profile (MYMOP2)

3.4. Endpoints

3.4.1. Primary endpoints

- Genetic variants in the genes of SOD1, C9orf72, FUS and TARDBP

3.4.2. Additional endpoints

- The following additional endpoints will be explored:

Demographic data, disease history and social setting
- Age, gender, place of residence
- Disease onset and duration
- Education, employment, housing

Family history of ALS and FTD
- Family members living with ALS or FTD
- Family members who have died from ALS or FTD

Clinical classification
- ALS subtypes (classic ALS, progressive muscular atrophy (PMA) and primary lateral sclerosis (PLS)
- Type of onset (bulbar region, trunk or extremities)

Functional deficit and progression
- ALS Functional Rating Scale (ALS-FRS)
- ALS progression rate (loss of ALS-FRS per months)
- King's classification of clinical stages of ALS
- Serum concentration of neurofilament light chain (sNfL)

Interventions and health care measures
- Percutaneous endoscopic gastrostomy (PEG)
- Non-invasive ventilation
- Tracheostomy
- Provision with assistive technology devices
- Symptomatic pharmacotherapy
- Physical, occupational and speech therapy

Patient´s expectations towards ALS therapy
- Measure Your Medical Outcome Profile (MYMOP2)

This evaluation is exploratory. There is no formal hypothesis that is tested.

4. Overall study design

4.1. Study design

This is a longitudinal, non-interventional, non-randomized, multicenter, prospective study conducted in subjects with ALS. Duration of study participation for each subject will be up to approximately 12 months. Subjects will be enrolled to receive questionnaires, in order to assess the variables and to provide blood samples for molecular genetic testing. Approximately 1,000 subjects are planned to complete the study. It is anticipated that up to approximately 18 sites will be activated in Germany. This registry study will be reported according to STROBE-statement.

4.2. Participating centers

The study follows a multicenter research trial. Results we be conducted at approximately 18 ALS centers in Germany participating in the observation study. ALS centers in different geographical regions of Germany will be activated:

- Northern Germany: Berlin, Hannover, Rostock, Lübeck
- Eastern Germany: Dresden, Jena, Halle, Leipzig
- Western Germany: Essen, Bonn, Göttingen, Münster, Bochum,
- Southern Germany: Ulm, München, Mannheim

4.3. Overall study duration and assessments

The study will include ALS patients at specialized outpatient clinics (study sites). All subjects will undergo 3 assessments over a period of approximately 12 months. The assessment schedule will be as follows:

- Assessment at baseline: initial assessment of subjects including blood sampling and molecular genetic analysis
- Assessment at follow-up: follow-up assessment that is realized in a 6-month interval
- Assessment at the end of the study: final assessment after 10 to 14 months interval

and optional

- Assessment for interims analysis: interim analyses performed for this study at variable time points, at least after all subjects complete the 6-month assessments.

4.4. Study stopping rules

Not applicable for an observational study.

5. Study subjects

5.1. Number of study subjects

2,000 subjects are planned to be recruited. More than 1000 subjects are expected to complete the end-of-study assessments, after an observation period of 12 months.

5.2. Inclusion criteria

Being eligible to participate in this study, study candidates must meet the following eligibility criteria at the baseline assessment:

- ALS, including classical ALS, Progressive Muscle atrophy (PMA) or Primary Lateral Sclerosis (PLS)
- Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations
- Age of 18 years old at the time of informed consent

5.3. Exclusion criteria

- Inability to provide patient´s directives about the notification of individual study results on genetic variants of SOD1, C9orf72, FUS and TARDBP
- Inability to comply with study requirements
- Unspecified reasons that, in the opinion of the site investigator, perceiving the subject unsuitable for enrollment

6. Enrollment of subjects

The enrollment of subjects takes place in specialized ALS-outpatient centers in Germany. ALS patients being eligible for the investigation, will be invited to participate in this cohort study. After obtaining informed consent, subjects will be enrolled in the study. Approximately, 2,000 subjects will be observed in this study. Participating sites will be informed once 2,000 subjects have been enrolled.

7. Withdrawal of subjects

Subjects must be withdrawn from the study for any one of the following reasons:

- The subject withdraws informed consent
- The subject is unwilling or unable to comply with the protocol
- At the discretion of the investigator

The reason for the subject's withdrawal from the study must be recorded. In case of withdrawal before the end of the genetic investigation, another patient can be enrolled to surrogate the other.

8. Study procedures and data processing

8.1. Study procedures

Subjects will be registered at baseline, after the investigator has verified the eligibility of the subjects by means of inclusion and exclusion criteria. After obtaining informed consent, all data defined in the protocol will be collected from different sources:

- Data capture from medical records (registry): clinical characteristics, family history, interventions and health care measures
- Assessment and data capture at study site (on-site assessment): clinical characteristics, family history, interventions and health care measures, self-assessment scales (ALS-FRS, MYMOP)
- Assessment and data capture from remote (digital self-assessment): self-assessment scales (ALS-FRS, MYMOP)
- Assessment and data capture at molecular genetic laboratory (genetic analysis): genetic variants in the genes of SOD1, C9orf72, FUS and TARDBP
- Capture from APST platform (registry): provision with assistive technology devices

8.2. Data collection

Data will be collected from various sources and by different means. Some data are obtainable retrospectively as from medical records (at study sites) and platform-based registry (APST platform). Other data will be collected prospectively using on-site or assessments.

Data defined in the protocol will be assessed and captured by different means:

- Data from medical records and on-site assessments: data on clinical characteristics, family history, interventions and health care measures) will be collected on data sheets and transferred to predefined data fields on the web-based study software "studioMED+" or may captured on the electronic case report form (eCRF) of "studioMED+" directly.
- Data from remote assessment: data from digital self-assessments (ALS-FRS, MYMOP) will be captured on a smart phone application ("ALS-App") and stored in the data base of the APST platform (https://www.ambulanzpartner.de/). The "ALS-App" serves as a mobile application of the APST platform.
- Data from genetic laboratory: molecular genetic analysis will be performed on blood samples provided by study participant. Results from the genetic investigation will be generated by the genetic laboratory and transferred to predefined data fields on the web-based study software "studioMED+".
- Data on health care measures: data on the provision with assistive technology (complex power wheelchairs, communication devices, robotic assistive systems, symptomatic pharmacotherapy, physical, occupational and speech therapy will be captured on the APST platform directly.

8.3. Molecular genetic analysis

Molecular genetic analysis will be performed by a qualified and certified (ISO15189) laboratory. The procedures undertaken include DNA isolation from blood samples collected in EDTA tubes and DNA quality analysis. QF-PCR and RT-PCR analysis of the C9orf72 will be performed for repeat expansion analysis. Pathogenic repeat expansions as determined by PCR will be confirmed by Southern blot. Molecular genetic analysis of SOD1, FUS and TARDBP Will be carried out by sequencing of the coding region of the SOD1, FUS and TARDBP gene. Bioinformatics, diagnostic analysis, confirmation of the positive result in an independent experiment, as well as interpretation of genetic variants will be delivered by the service provider. The molecular genetic analysis and all associated services will be provided by ARCHIMED Life Science GmbH (ARCHIMEDlife), Vienna (Austria).

9. Assessments

9.1. Demographic data

Demographic data will be collected as follows:

Table 2: Items used to describe demographic data

Item	Description
Date of Birth	MM/YYYY
Gender	Male Female
Place of residence	PLZ (first 3 digits), NNNXX

9.2. Social characteristics

Data on social characteristics will be collected as follows:

Table 3: Items used to describe social characteristics

Item	Description
Marital status	married single divorced widowed
Highest level of education	No formal education Primary school Secondary school Advanced or higher certificate Bachelor's degree or national diploma Postgraduate diploma/Master's degree Doctorate (PhD)
Employment status	Student Working for payment or profit Unemployed Retired from employment Looking after home/family Unable to work due to permanent sickness or disability Other (Please specify)
Working hours in employment	Working hours per week
Living arrangement	Own home Assisted living Nursing home Hospice

9.3. Disease history

Data on disease history will be collected as follows. Onset of ALS will be defined at time of paresis in extremities, dysarthria or dysphagia.

Table 4: Items used to describe the disease history

Item	**Description**
Date of onset	MM-YYYY
Date of diagnosis	MM-YYYY
Age of onset	YY
Duration of disease	MM
Data of death (if applicable)	MM-YYYY

9.4. Family history

The number and degree of relatedness of family members who are living with ALS (or FTD) or who died of ALS (FTD) will be investigated. Furthermore, family members suffering from any neurological/psychiatric disorder or who died of any neurological/psychiatric disorder will be determined. A first-degree relative (FDR) is a person's parent (father or mother), full sibling (brother or sister) or child. It constitutes a category of family members that largely overlaps with the term nuclear family, but without spouses. A second-degree relative (SDR) is someone who shares 25% of a person's genes. It includes uncles, aunts, nephews, nieces, grand-parents, grandchildren, half-siblings, and double cousins.

Table 5: Items used to describe the family history of ALS or FTD

Item	1st degree relative (n)	2nd degree relative (n)
ALS (living)	Suspected Probable Definite Genetically confirmed	Suspected Probable Definite Genetically confirmed
ALS (deceased)	Suspected Probable Definite Genetically confirmed	Suspected Probable Definite Genetically confirmed
FTD (living)	Suspected Probable Definite Genetically confirmed	Suspected Probable Definite Genetically confirmed
FTD (deceased)	Suspected Probable Definite Genetically confirmed	Suspected Probable Definite Genetically confirmed
Neurological/psychiatric disorder (living)	Definite	Definite
Neurological/psychiatric disorder (deceased)	Definite	Definite

n = number of individuals

9.5. Clinical classification

Data on clinical classification will be collected as follows:

Table 6: Items used to describe clinical classification

Item	Description
ALS subtypes (domination of upper or lower motor neuron)	Classical ALS Progressive Muscle Atrophy (PMA) Primary Lateral Sclerosis (PLS)
Type of onset (region of onset)	Bulbar region Trunk Upper extremities Lower extremities

9.6. Functional deficits and progression

9.6.1. ALS Functional Rating Scale

The functional impairment will be described by using the ALS functional rating scale (ALS-FRS). The ALS-FRS is a questionnaire that is frequently used in ALS, in order to describe functional impairment (Cedarbaum et al. 1999). Furthermore, motoric function and skills of arms and legs, the bulbar function as well as the respiratory function is described. Interventions in the areas of nutrition and ventilation as well as the ability to use communication devices are also targeted. The questionnaire contains 12 short, clear questions, each with five possible answers (0-4). In total, 0 to 48 points can be achieved. The lower the number of points achieved, the higher the defined degree of severity of the functional impairment. The online assessment of ALS-FRS complements the well-established face-to-face application of the ALS-FRS (Maier et al. 2012).

9.6.2. ALS progression rate

The ALS progression rate (∆ALS-FRS) can be derived from the ALS-FRS. The loss of ALS-FRS value per month, or delta ALS-FRS, indicates the rate of deterioration and predicts survival (Kimura et al. 2006). ∆ALS-FRS is calculated using the following formula:

$$\Delta\text{ALS-FRS} = \frac{(48 - \text{ALSFRSR})}{\text{Duration of disease since diagnosis (months)}}$$

9.6.3. King´s clinical stage of ALS

The course of disease was classified according to the King´s clinical stage of ALS (Balendra et al. 2014). Stage 1: involvement of one clinical region; Stage 2: involvement of second clinical region; Stage 3: involvement of third clinical region; Stage 4: nutritional or respiratory failure.

Table 7: Items used to describe functional deficits and progression

Item	Description
ALS-FRS	ALS-FRS, total score ALS-FRS, score points per item (1-12)
ALS progression rate	Loss of ALS-FRS score points per month
King´s clinical ALS stages	Stage 1-4

Neurofilament light chain (sNfL)	Serum concentration of neurofilament light chain (sNfL) in pg/mL

9.7. Interventions and health care measures

Data on clinical interventions and health care measures will be collected as follows:

Table 8: Items used to describe clinical interventions and health care measures

Item	**Description**
Percutaneous endoscopic gastrostomy (PEG)	Y/N Date of provision (MM/YYYY)
Non-invasive ventilation (NIV)	Y/N Date of provision (MM/YYYY) Usage up to 8 hours per day Usage 8 to 16 hours per day Usage more than 16 hours per day
Invasive ventilation (IV)	Y/N Date of provision (MM/YYYY)
Provision of manual wheelchair (1)	Y/N Date of provision (MM/YYYY)
Provision of complex power wheelchair (1)	Y/N Date of provision (MM/YYYY)
Provision of augmented communication device (1)	Y/N Date of provision (MM/YYYY)
Provision of assistive technology (e. g. robotic arms), (1)	Y/N Date of provision (MM/YYYY)
Physical therapy (2)	Y/N Treatment units per week
Occupational therapy (2)	Y/N Treatment units per week
Speech and swallowing therapy (2)	Y/N Treatment units per week
Pharmacological therapy (3)	Riluzol, Y/N Symptomatic drugs, number of medicines

(1) Data will be obtained in a multi-center subset of up to 300 participants
(2) Data will be obtained in a single-center subset of up to 100 participants
(3) Data will be obtained in a multi-center subset of up to 200 participants

9.8. Patient´s expectations towards ALS therapy

Treatment expectations will be assessed by the Measure Yourself Medical Outcome Profile (MYMOP2, Hermann et al., 2014, Monnery et al., 2018, Ishaque et al., 2019). The MYMOP is a brief, patient-generated, problem-specific questionnaire, which requires participants to qualify – and by that means prioritize – bothersome symptoms or impairments. The MYMOP consists of four questions and is a brief, patient-generated, problem-specific questionnaire. The first two questions require participants to specify symptoms that concern them most. Sub-

sequently, participants evaluate the severity of this symptom on a 7-point Likert scale (e.g., weakness of the right leg could score 0 for “as good as it could be” to 6 for “as bad as it could be”). The third question of the questionnaire uses the same 7-point Likert scale to assess whether the symptom is limiting or preventing a daily activity (such as walking). In the fourth question participants rate their general well-being. All domains (symptom severity, restriction of activity, and general well-being) can be analyzed individually or as a total score.

Table 9: Items used to describe patient’s expectations towards ALS therapy

Item	**Description**
Symptom 1	Qualitative description Likert scale 0-6
Symptom 2	Qualitative description Likert scale 0-6
Activity	Qualitative description Likert scale 0-6
Well-Being	Likert scale 0-6

9.9. Genetic data

Each of the following genes will be tested: SOD1, C9orf72, FUS and TARDBP. Where applicable, detailed information about the mutation (e. g. expansion, expansion number, substitution and location, deletion/duplication and location) will be collected along with an assessment of pathogenicity as adjudicated by the laboratory (e. g. benign, likely benign, likely pathogenic, pathogenic, variant of uncertain significance).

Table 10: Description of the genes and respective mutation type

Gene	**Variant**	**Mutation type**	**Interpretation and classification**
SOD1	Y/N	Substitution Deletion Insertion Duplication Inversion	Benign Likely Benign Likely Pathogenic Pathogenic Variant of Uncertain Significance
C9orf72	Y/N	Expansion	Benign Pathogenic
FUS	Y/N	Substitution Deletion Insertion Duplication Inversion	Benign Likely Benign Likely Pathogenic Pathogenic Variant of Uncertain Significance
TARDBP	Y/N	Substitution Deletion Insertion Duplication Inversion	Benign Likely Benign Likely Pathogenic Pathogenic Variant of Uncertain Significance

10. Quality assurance

10.1. Data quality

During and/or after completion of the registry, quality assurance officers named by APST or the regulatory authorities may wish to perform onsite audits. The Investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested. Data quality is facilitated on a web-based secure clinical research software (studioMED+, Germany) that encompasses a study management component and an electronic case report form (eCRF). It digitally enables the multi-step workflow of data capture linking all data entry roles at participating ALS centers. At the studioMED+ software, the data from all different data sources are captured and processed.

10.2. Review of data

The study software studioMED+ is used as a data management system in this study and enables the storage and tracking of study data, especially study visits, by means of an electronic case report form (eCRF). StudioMED+ provides study-related documents and an overview of all study patients. Received data will be controlled for completeness using the studioMED+ study software. The reporting tool of the same software will be used to report registry numbers and collected data at regular intervals (monthly).

10.3. Genetic review board

A review board on genetic results will be implemented. The genetic review board will serve as a consulting body for the interpretation of complex or uncertain genetic research results. This refers mostly to result in the categories "likely pathogenic and “variant of uncertain significance” (details in 9.9). The genetic review board comprises of the following members:

- Prof. Dr. Jochen Weishaupt, Mannheim University Hospital, certified neurologist and expert in ALS genetics
- Prof. Dr. Denise Horn, Charité – Universitätsmedizin Berlin, certified geneticist, expert in genetic consulting
- PD Dr. Peter Körtvélyessy, Charité – Universitätsmedizin Berlin, certified neurologist and expert in neurogenetic consulting

11. Statistical methods and analysis plan

Descriptive statistics will be presented for each assessment of all subjects at study visit. Subgroup analyses by genetic or clinical criteria or other baseline characteristics will be performed. Secondary endpoints in the genetically defined subsets of ALS with confirmed SOD1 or C9orf72 mutations will be compared to genetically tested patients with ALS not revealing any ALS-associated mutation in any of the tested genes. Descriptive statistics will be used for the statistical analysis (frequency in percentage, mean, median, standard deviation in ±, interquartile ranges (Q1, Q3), and ranges (min, max). The standardized mean difference (SMD) will be applied in this study. The SMD of each measure over up to 12 months will be estimated using the change in measure between each subject’s assessments and within each individual. The standardized mean difference expresses the size of intervention effect. Difference of frequencies between two groups will be assessed by Fisher’s exact test or Chi-square test, or within metric data by using the Shapiro–Wilk test, Kruskal–Wallis test and Mann–Whitney U-test. The Wilcoxon test will be employed for the analysis of statistical power of ordinally-scaled data, while metric data were subjected to the t-test (ALS-FRS, MYMOP). This analysis applies to the comparison of genetically defined subsets of ALS (baseline characteristics and changes over time). The analysis of follow-up data is limited to complete

cases, since not all patients are expected to complete end-of-study assessments due to disease progression, e.g., death. It is aimed to compare the baseline characteristics and the proportion of death between those who completed and not those not completed 6 months and 12-month assessment. Statistical significance will be ascertained by according to an error risk of up to 5% (p-value < 0.05). Associations for the clinical outcomes will be assessed by linear regression models adjusted for potential cofounding factors. Results of the longitudinal observations will be also controlled for the influence of any covariate (sex, age, intervention history). Longitudinal analysis by means of group comparisons will be applied by using a multivariate analysis. 95% confidence intervals with p-values will be reported. In order to draw conclusions from the samples with censored data, missing data records will be omitted and treated as missing values. Data analysis will be performed using SPSS (Version 25.0).

12. Ethical and legal principles

12.1. Ethical and regulatory requirements

APST must comply with all instructions, regulations, and agreements in this protocol and applicable ICH and GCP guidelines and conduct the observational study according to local regulations. The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

12.2. Responsibilities of the investigator

The observational study is realized in collaboration of APST and Charité – Universitätsmedizin Berlin. The study protocol will be approved by the Independent Medical Ethics Committee (IEC) of the Charité – Universitätsmedizin Berlin, Germany. The protocol, and other required study documents must be approved prior to starting the study. It is the responsibility of the investigator to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations. APST must receive a letter documenting ethics committee approval, which specifically identifies the amendments prior to the initiation of the study.

12.3. Informed consent procedures

12.3.1. Informed consent procedures of study participants

Prior to any data collection informed consent will be obtained from all eligible and participating patients. Information about the study and that study participation is voluntary will be explained to the subject. The informed procedure will be organized in a multi-step process of 1) patient information, 2) genetic counselling prior to study participation, 3) written informed consent and selection of modalities for the notification of genetic study results. The patient information encompasses the option, that study participants are, however, entitled to refuse genetic counselling in writing, if they have already been informed about its content. The study information and the offered genetic counselling will address the potential medical, psychological and social burden that may be associated with pathogenic gene mutations as well as the individual or societal benefits aimed with the study. Participating patients will decide to provide blood samples for the following research purposes:

- Use for exclusive analysis of the genes SOD1, C9orf72, FUS and TARDBP as defined in this protocol
- Optional and future use for analysis of other known ALS-related genes
- Optional and future use for the search of still unknown ALS-related genes

The subject must be given sufficient time to consider, whether to participate in the study. A copy of the informed consent, signed and dated by the subject, will be given to the subject. Confirmation of a subject's informed consent will also be documented in the subject's medical record prior to any data collection under this protocol. The signed informed consent will be retained with the study records. The informed consent procedure will be performed in alignment with the "Genetic Diagnosis Act" (Gendiagnostikgesetz, GenDG).

Given the potential, diagnostic and therapeutic relevance of individual study results on genetic variants of SOD1, C9orf72, FUS and TARDBP genes, all study participants are offered the principal option to be informed about the result of genetic investigation. Conversely, the knowledge and awareness about own study results – encompassing the potential implications for genetically related family members – might be perceived as psychologically burdensome. Therefore, study participants will be informed about the requirement to select between notification options of their individual study results. Study participants who decided to be notified about the genetic study results are offered to seek genetic consultation prior to the notification of study results. The offered genetic consultation will include the information on the mutation type, the interpretation of results (benign, likely benign, likely pathogenic, pathogenic or variant of uncertain significance) as well as the potential medical, psychological and social implications of the findings. The procedure of genetic counseling is described in more detail in section 12.3.3. Study participants will be informed that genetic study results of uncertain significance may be discussed within the genetic review board which is described in section 10.3. The patient´s directive concerning the notification about the individual study results is subject to the study information and mandatory part of the informed consent. Study participants are requested to select one of the following options of notification about individual study results:

- No notification about genetic study results
- Notification about all genetic study results
- Notification about selected genetic study results with therapeutic relevance

Patients who refuse to be notified about study results will not be informed about the outcome of genetic analysis. This patient´s directive explicitly includes pathogenic mutations that might be of diagnostic or therapeutic relevance. The patient´s directive of notification of all genetic study results will include normal findings (no or benign variants) genetic, genetic variants of unknown significance and pathogenetic mutations (likely pathogenic or pathogenic genetic variants in the investigated genes of SOD1, C9orf72, FUS and TARDBP. Results of diagnostic relevance are defined as genetic variants being known to cause ALS or can increase the risk of ALS or can modify the phenotype of the disease including the progression rate. The finding of pathogenic variants can lead to the diagnosis of fALS although the disorder – given the negative family history of ALS – has prior been classified as sALS. The diagnostic relevance can extend to other family members as likely pathogenic of pathogenic mutations in the study at ALS genes might substantiate a genetic risk for ALS to first- and second-degree relatives of study participants. Therapeutic relevance is defined by the planning or performance of a phase 3 clinical trial, a planned or ongoing early access program or an expected approval of genetic medicine targeting one of the studied genes within the next 12 months. Currently, therapeutic relevance can be stated for mutations found in the SOD1 gene. Therapeutic relevance of C9orf72 and FUS can be expected within the next few years post-approval of this study protocol. The definition of diagnostic and therapeutic relevance and the scheme of notification of individual study results is provided in table 11.

12.3.2. Genetic consultation on genetic study results

All study participants are offered the principal option to seek genetic consulting. Genetic counseling on study participation (prior to genetic testing) and prior to the notification of study results (after genetic testing) will be differentiated (Table 11). The counseling prior entering the study will be performed by the study neurologist. However, under certain circumstances, such as the family history of fALS, the additional counseling by a neurologist being certified for genetic counseling or by a certified geneticist can be required. The consultation prior participating in the study will include the potential medical, psychological and social implications that can be associated with pathogenic gene mutations as well as the potential individual treatment options indicating gene-specific treatment options, which are available or in clinical development.

Study participants will be offered a genetic consultation on the genetic study results. In principle, study results showing no genetic variants or benign variants will lead to the study neurologist consulting about the specific results. In contrast, study results of *likely pathogenic* or *pathogenic mutations* will be primarily consulted by the study neurologist, in order to refer the patient to a specialized neurologist being certified for genetic counseling or to a certified geneticist. Recruiting study sites are prepared to refer patients (or their advice seeking relatives) to certified geneticists who are experienced in the consultation on genetic variants in ALS. In preparation of external genetic consultation, patients are provided with a sealed envelope containing the pseudonymized study results. Subsequently, the patient will forward the envelope to the genetic consultant. The genetic consultant can contact the study center for additional clinical information and might decide for an independent genetic investigation, in order to confirm the study results. The confirmation can be done by retesting or, preferably, by means of de-pseudonymization of study results. As authorized by the study participant – upon request of consulting geneticist – the genetic study results might be de-pseudonymized by the study center. Based on the de-pseudonymization order, the unblinded genetic report on SOD1, C9orf72, FUS and TARDBP will be provided by genetic laboratory and used for genetic consultation. The unblinded genetic results are suitable for genetic consulting, such as the laboratory ARCHIMED Life Science GmbH (ARCHIMEDlife, Vienna, Austria). ARCHIMEDlife complies to all required certifications for genetic analysis (including ISO15189). Thus, the genetic results – primarily generated for research purposes – allow the unrestricted use for genetic counseling.

Table 11: Differentiated notification of study results in relation to patients´ directives

Informed consent	**Genetic consulting prior study participation**	**Patient´s directive on notification about genetic results**	**Genetic result**	**Genetic consulting on genetic results**
informed consent of all patients as obtained by study neurologist	refusal of genetic consultation	no notification about genetic results	not applicable	not applicable
	genetic counselling on the po-	notification about all genetic results	• no variant • benign variant	counseling by study neurologist

	tential burden of pathogenic gene mutations and the potential diagnostic and therapeutic measures as offered by study neurologist (sALS) or certified geneticist (fALS)		• uncertain significance • likely benign • likely pathogenic • pathogenic	counseling by study neurologist followed by geneticist
		notification about genetic results with <u>therapeutic relevance</u>	• likely pathogenic • pathogenic variant with treatment option	counseling by study neurologist followed by geneticist

12.3.3. Informed consent procedures of first and second-degree relatives

Study results on genetic variants of SOD1, C9orf72, FUS and TARDBP genes might be of diagnostic and therapeutic relevance of study participant´s first and second-degree relatives. Relatives may include individuals with symptoms of ALS or FTD (established or probable diagnosis of fALS) as well as asymptomatic individuals (unknown risk of ALS). In principle, study participants are offered to provide the genetic study results to authorized family members. However, the knowledge and awareness about genetic research of study participants might be perceived as psychologically burdensome for first and second-degree relatives. The information includes the advice of genetic counseling prior to the notification of genetic study results. The study information and the offered genetic counselling will address the potential medical, psychological and social burden that can be associated with pathogenic gene mutations as well as the individual or societal benefits aimed with the study. Therefore, the provision of the study participant´s genetic study results will be restricted and must comply with the following requirements:

- Authority for provision of study results to first and second-degree relatives by the study participant in a written manner
- Written information to first or second-degree relatives on the option of receiving genetic results of study participant
- Genetic counseling of first or second-degree relatives prior to signing informed consent on receiving genetic results of study participant
- Informed consent of first or second-degree relatives for receiving the study participant´s genetic study results
- Directives of first or second-degree relative about the notification criteria of study participant´s genetic results

The relative´s directives concerning the notification criteria is part of the informed consent procedure. The notification criteria for relatives are the same as for the patient (see Table 12). The study results might be provided to authorized first and second-degree relatives after the death of the study participant (postmortem provision of participant´s genetic study results).

Table 12: Differentiated provision of genetic study results to first and second-degree relatives and modes of notification

Patient´s directive	**Notification**	**Provision of study results**
<u>no</u> notification	not applicable	not applicable
notification about <u>all</u> individual study results	by request of relative	provision of study results to genetic consultant for subsequent use in genetic counseling

notification about selected study results with therapeutic relevance	by study center	Counseling by study neurologist and referral to genetic consultant

12.3.4. Genetic consultation of first and second-degree relatives

First and second-degree relatives of study participants will be advised for genetic counseling 1) prior to signing the informed consent on receiving genetic results of study participant and 2) prior to notification of study participant´s genetic results (when the relative has signed the informed consent). The subject of the counseling will be differentiated according to the patient's directives and the genetic study results. An overview on the scheme of genetic counseling is provided in Table 12. As part of the study, recruiting study sites are prepared to refer patients (or their advice seeking relatives) to certified geneticists who are experienced in the consultation on genetic variants in ALS. The genetic results of the study participant will be provided by the study on request of the genetic consultant and used for counseling of first and second-degree relatives. In case that study results are of therapeutic relevance, first and second-degree relatives will be actively informed by study center and invited respectively to genetic counseling by the study neurologist. Subsequently, a referral to a certified geneticist will be offered. For referral, the relative will receive study results being handed over to the certified geneticist. The genetic counseling of the first and second- degree relatives is considered independent from this observational study and is not subject of this study protocol.

12.3.5. Follow-up on study results with therapeutic relevance

Therapeutic relevance is defined by the planning or performance of a phase 3 clinical trial, a planned or ongoing early access program or an expected approval of a genetic medicine targeting one of the studied genes within the next 12 months. The principal investigator and the genetic review board will analyze, review and interpret published information on the planning, beginning and completion of phase 3 clinical trials, early access programs or approvals of genetic medicines targeting one of the studied genes. The therapeutic residence will be defined as described at least every 12 months for 3 years after the beginning of the study. The extension of this review activity is of great scientific and medical value and will be subject of further investigations and related protocols.

12.4. Insurance and reimbursement

Not applicable for an observational study.

12.5. Data protection and confidentiality

The subject will not be identified by name in any of study reports being solely used for research purpose. The ethics committees, and various government health agencies can inspect the records of this study. Every effort will be made to keep the subjects´ personal medical data confidential. This register study is subject to the regulations set forth in the Data Protection Act which shall be fully adhered to. APST and the Charité agreed on the Order Data Processing (ODP) Agreement in accordance with Council of the European Union General Data Protection Regulation (EC-GDPR; transl: *EU-Datenschutzgrundverordnung*, *EU-DSGVO*). The patient data shall be pseudonymized for further processing and statistical analysis. For this purpose, the patient data shall be encoded. Data assessment shall take place exclusively using the encoded (pseudonymized) data sets so as to exclude any tracing of an individual patient's identity. Data pseudonymization shall be performed in accordance with the regulations set forth in the general data protection regulation (§ 4 clause 5 DSGVO). The APST shall be responsible for the storage and processing of patient data that have previously been captured via the study software (studioMED+). The patient data is stored in an encrypted and pseudonymized pattern

in a database on its own root server in Germany. In addition, a principle of roles and rights is integrated, which guarantees decryption and de-pseudonymization only for authorized persons.

12.6. Access rights to personal data

Participants in the study are entitled to view any of their personal data captured in the context of the study. At that, patients themselves – or their authorized proxy - are granted the option to receive a print copy of all the data captured on clinical research software (studioMED+). Patients are furthermore entitled to notify us of any errors in the data captured on them and to request data correction.

12.7. Archiving

Data from all different primary data sources (see 8.3) shall be captured and stored on the clinical research software (studioMED+). Any data from questionnaires that have been filled in manually shall be transferred to the eCRF component of studioMED+. All the data shall be pseudonymized and transferred to suitable computer programs for statistical evaluation. Following statistical analysis, the results shall be illustrated and published as tables, graphs, and in text format. The publishing of the results shall take place in strict observation of the DSGVO, thus excluding the possibility of tracing an individual patient's identity. The pseudonymization of data excludes by guarantee any direct or indirect linking of data to personal patient information and the identification of individual patients. The pseudonymized cohort study data used for statistical and scientific purposes are not subject to any data retention or erasure period. The data captured in the context of this study shall be retained for a minimum of 10 years following study completion. Data erasure is not envisaged with the objective of upholding care research in the long term. The erasure of single data sets is exempt from this regulation and shall be performed upon the respective patient's request or upon withdrawal of the respective patient's consent to participating in the study at any time and without giving reasons.

13. Reports

13.1. Internal reports

Reports on the study will be generated on a monthly base. The reports will provide information about the number of registered patients and delivered genetic investigations per study center.

13.2. Interim report

Interim analyses performed for this study at variable time points, at least after all subjects complete the 6-month assessments.

13.3. Publication of results

The main results of the study will be published in a peer-review journal.

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