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CLINICAL RESEARCH ARTICLE

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Clinical and patient-reported outcomes and neurofilament response during tofersen treatment in *SOD1*-related ALS—A multicenter observational study over 18 months

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Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS functional rating scale—revised; ALS-PR, ALS progression rate; EAP, expanded access programs; MYMOP, Measure Yourself Medical Outcome Profile; NfL, neurofilament light chain; NPS, Net Promoter Score; PRO, patient-reported outcomes; sNfL, serum neurofilament light chain; SOD1, superoxide dismutase 1; SVC, slow vital capacity; TSQM-9, Treatment Satisfaction Questionnaire for Medication.

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Abstract

Introduction/Aims: In amyotrophic lateral sclerosis (ALS) caused by *SOD1* mutations (SOD1-ALS), tofersen received accelerated approval in the United States and is available via expanded access programs (EAP) outside the United States. This multicenter study investigates clinical and patient-reported outcomes (PRO) and serum neurofilament light chain (sNfL) during tofersen treatment in an EAP in Germany.

Methods: Sixteen SOD1-ALS patients receiving tofersen for at least 6 months were analyzed. The ALS progression rate (ALS-PR), as measured by the monthly change of the ALS functional rating scale—revised (ALSFRS-R), slow vital capacity (SVC), and sNfL were investigated. PRO included the Measure Yourself Medical Outcome Profile (MYMOP2), Treatment Satisfaction Questionnaire for Medication (TSQM-9), and Net Promoter Score (NPS).

Results: Mean tofersen treatment was 11 months (6–18 months). ALS-PR showed a mean change of −0.2 (range 0 to −1.1) and relative reduction by 25%. Seven patients demonstrated increased ALSFRS-R. SVC was stable (mean 88%, range −15% to +28%). sNfL decreased in all patients except one heterozygous *D91A-SOD1* mutation carrier (mean change of sNfL −58%, range −91 to +27%, $p < .01$). MYMOP2 indicated improved symptom severity ($n = 10$) or yet perception of partial response ($n = 6$). TSQM-9 showed high global treatment satisfaction (mean 83, SD 16) although the convenience of drug administration was modest (mean 50, SD 27). NPS revealed a very high recommendation rate for tofersen (NPS +80).

Discussion: Data from this EAP supported the clinical and sNfL response to tofersen in SOD1-ALS. PRO suggested a favorable patient perception of tofersen treatment in clinical practice.

KEYWORDS
amyotrophic lateral sclerosis (ALS), clinical course, neurofilament light chain (NfL), patient-reported outcomes, tofersen

1 | INTRODUCTION

In amyotrophic lateral sclerosis (ALS), approximately 2% of patients carry disease-causative mutations in the superoxide dismutase 1 (*SOD1*) gene.[1,2] Tofersen is the first intrathecally delivered RNase H antisense oligonucleotide leading to a RNase-H dependent degradation of the *SOD1*-messenger RNA and reduction of SOD1 protein levels.[3,4] On April 25, 2023, the U.S. Food and Drug Administration (FDA) granted accelerated approval for the treatment of adult patients with mutations in the *SOD1* gene. Approval was granted based on the results of a phase 3 trial (VALOR study) and open-label extension (OLE) study.[5,6] The trial failed to demonstrate a significant slowing of ALS progression as measured by the ALS functional rating scale—revised (ALSFRS-R), the primary endpoint of this study. More specifically, a significant reduction in the slope of ALSFRS-R at 28 weeks was not met, however there were reductions in CSF SOD1 protein levels and neurofilament light chain (NfL) indicating target engagement and reduction in neuroaxonal loss, respectively. At 52 weeks, earlier initiation of tofersen was associated with less decline in functional measures including ALSFRS-R, slow vital capacity (SVC), and handheld dynamometry compared to the delayed start open label extension (OLE) cohort.[5] However, the OLE design did not allow direct comparison with the placebo group, which limited the interpretation. In the view of the established role of NfL as progression biomarker of ALS, the impact of tofersen on NfL levels was—and increasingly is—an important outcome parameter for assessing the therapeutic efficacy of this drug.[5,7–17]

Outside of clinical trials, tofersen might be used in patients with a wide spectrum of clinical findings, ranging from slow ALS progression and high functional status to faster progression and low functional status. At both ends of the spectrum, the ALSFRS-R has methodological limitations in demonstrating a treatment response. Because of this, serum NfL (sNfL) was of particular interest to

provide valuable information on tofersen treatment response in clinical practice.[16,17] Despite its methodological limitations, the ALSFRS-R became an accepted primary endpoint in clinical trials and established measure of functional impairment.[18] Furthermore, the monthly slope of the ALSFRS-R was used to calculate the ALS progression rate (ALS-PR).[5,16,19] In recent years, the ALSFRS-R has been increasingly used as a self-assessment tool.[20–26] The option for patients to collect the ALSFRS-R themselves represents an additional source for ALSFRS-R data. Remote digital assessment allowed ALSFRS-R data to be captured between clinic visits—or even from patients receiving tofersen treatment outside of academic centers.[20,21]

Tofersen treatment comes with considerable patient burden that is primarily related to the monthly intrathecal administration of the drug. Therefore, the subjective treatment perception from a patient's perspective and the assessment of patient-reported outcomes (PROs) are important objectives of future studies and this investigation.[25–28]

In Germany, an expanded access program (EAP) of tofersen was introduced in January 2022. For patients receiving tofersen in clinical practice, data on clinical and genetic characteristics, the ALSFRS-R, ALS-PR, SVC, and NfL were systematically assessed. In addition, three PROs were obtained to measure individual expectations and experiences of therapy (Measure Yourself Medical Outcome Profile, MYMOP2), treatment satisfaction (Treatment Satisfaction Questionnaire for Medication, TSQM 9) and patients' recommendations of therapy (Net Promoter Score, NPS).[29–35]

When analyzing existing data of tofersen treatment, this study aims to: (1) investigate the clinical and genetic characteristics of an EAP cohort with inclusion and exclusion criteria beyond those of the VALOR and OLE studies, (2) determine the frequency and extent of response to tofersen, (3) explore treatment expectations and the subjective perception of outcome, and (4) assess treatment satisfaction.

2 | METHODS

2.1 | Study design

This study is a secondary use of existing data from three multicenter studies, in which clinical, genetic, NfL and PRO data are collected. Data were obtained from (1) a registry of clinical characteristics, phenotypes, and the standard of care (ClinicalTrials.gov ID NCT05852418), (2) a large-scale longitudinal study on sNfL in ALS, and (3) a multicenter study on genetic variants in ALS (ClinicalTrials.gov ID NCT05852405).

2.2 | Studied cohort

Data analysis was performed in patients fulfilling three main criteria: (1) diagnosis of ALS, (2) harboring an *SOD1* mutation (*SOD1*-ALS), and (3) treatment with tofersen for at least 6 months.

2.3 | Setting

2.3.1 | Access to existing data

Patients at eight multidisciplinary ALS centers in Germany (Berlin, Bonn, Dresden, Erlangen, Hannover, Göttingen, Mannheim, and Münster) were identified. Data on clinical characteristics, ALSFRS-R, and NfL were obtained from the above-described observational studies.

2.3.2 | Data collection

Clinical and PRO data were captured monthly along with the tofersen treatment. Serum and CSF for NfL analysis were collected on the day of tofersen administration as part of standard of care. ALSFRS-R data were assessed by self-rating either on a printed form or using a smartphone application for remote digital data collection ("ALS-App").[20,21] Data were collected between October 2021 and August 2023.

2.3.3 | NfL analysis

sNfL concentrations were analyzed in a core facility at the ALS center in Berlin measured by means of the single molecule analysis technology (SIMOA) using the commercially available NfL advantage kit (Quanterix Inc., USA). Cerebrospinal fluid (CSF) NfL concentrations were measured at the Labor Berlin—Charité Vivantes GmbH using the NF-light ELISA (UmanDiagnostics, Sweden).

2.4 | Protocol approvals and registrations

The study protocols were approved by the Medical Ethics Committee of Charité—Universitätsmedizin Berlin, Germany under number EA2/168/20, EA1/128/21, and EA1/219/15. Written informed consent was obtained from all participants.

2.5 | Variables

2.5.1 | Clinical and genetic data

Clinical and genetic data included sex, age at symptom onset, disease duration, family history and genetic variants of the *SOD1* gene. Symptom onset was defined as the date (in month and year) of the onset of motor functional deficits: dysarthria, dysphagia, paresis or spasticity of limbs and trunk or respiratory symptoms. Disease duration was the number of months between symptom onset and the time of assessment.

2.5.2 | ALS functional rating scale—revised

ALSFRS-R is a validated instrument to assess functional impairment in ALS (Methods section of Supplement). The total range of

the scale spans 0 (poor function) to 48 scale points (full function).[18,19] ALSFRS-R pre-treatment was the total ALSFRS-R at the start of tofersen treatment whereas ALSFRS-R during treatment indicates the last measured value of the observation period.

2.5.3 | ALS progression rate

ALS-PR was measured from the time of onset and by the monthly slope of ALSFRS-R scale points as previously described. It was calculated using the following formula: (48-ALSFRS-R divided by disease duration (months)).[6] A classification of ALS-PR of slower ALS (<0.5 ALSFRS-R/month), intermediate ALS (≥0.5 and ≤1.0 ALSFRS-R/month) and faster ALS (>1.0 ALSFRS-R/month) progression was applied.[19] ALS-PR pre-treatment was calculated from the time of onset to the initiation of tofersen treatment. ALS-PR during treatment described ALS-PR from the time of onset to the last measured value of the observation period.

2.5.4 | Slow vital capacity

Data on SVC were normalized for sex, age, body weight, and height and given in percent of normal.

2.5.5 | Neurofilament light chain in serum

The sNfL concentration was analyzed before and during the tofersen treatment as described and referred to the time of sampling.

2.5.6 | Tofersen treatment duration

Treatment with tofersen was assessed as the number of months receiving tofersen.

2.5.7 | Measure Yourself Medical Outcome Profile

MYMOP2 is a patient generated scale for defining and then measuring individual treatment expectations and experiences.[29–31] This score is a problem-specific questionnaire, which—as a first step—requires participants to prioritize two symptoms or impairments that bother them most. Furthermore, participants were requested to choose one activity that is important to them, and that the disease makes difficult or prevents them from performing. In a second step, participants were requested to quantify the severity of symptoms and the impairment of activity on a 7-point Likert scale (0 for "as good as it could be" to 6 for "as bad as it could be").

2.5.8 | Response to treatment measured by MYMOP2

When evaluating response to treatment, prioritized symptoms and activities were separately investigated. Thus, patients showing an improvement in at least one of the two target symptoms—as assessed by MYMOP2—were defined as "responders" to tofersen. Participants with reported improvement or stabilization (unchanged rating) in one symptom and deterioration of the other qualified symptom were classified as "partial responders." Individuals reporting a deterioration in both target symptoms were defined as "non-responders." Patients showing an improvement in activity were defined as "responders" to tofersen. Participants with unchanged rating of activity were classified as "partial responders," whereas individuals with deteriorated activity level were defined as "non-responders."

2.5.9 | Treatment Satisfaction Questionnaire for Medication

TSQM 9 is a pre-defined and validated questionnaire concerning patient satisfaction with medication.[32–34] The score comprising nine questions is described in detail in the Methods section of the Supplement. The questions were answered on a five-point or seven-point scale (e.g., from very dissatisfied to very satisfied). Each of the nine questions was summed in a total score that can range from 0 to 100. A higher total score equates to greater satisfaction (calculation described in the Methods section of the Supplement).

2.5.10 | Net Promoter Score

NPS was used for examining patients' attitude toward their treatment with tofersen.[35] This metric was calculated based on responses to a single question: "How likely is it that you would recommend tofersen to a fellow SOD1-ALS patient?" Possible answers ranged from 0 (very unlikely recommendation) to 10 (very likely recommendation) points. Patients were considered as "promoters" (10 or 9 score points), as "passives" (8 or 7 points) or "detractors" (6 to 0 points). The NPS is calculated by subtracting the percentage of detractors from the percentage of promoters (calculation described in in the Methods section of the Supplement). A NPS with a positive value (>0) is regarded as a supporting recommendation.[35]

2.6 | Statistical methods

Descriptive statistics were used (frequency in percent, mean, median, and ranges) and data analyzed using Statplus (Version 7.7.11, AnalystSoft Inc., Walnut, CA, USA) and GraphPad Prism (Version 9.0.0 for Windows, GraphPad Software, San Diego, CA, USA). Mann–Whitney U test and repeated measures ANOVA with Greisser-Greenhouse correction were applied. Significant levels are defined with $p \leq .05$.

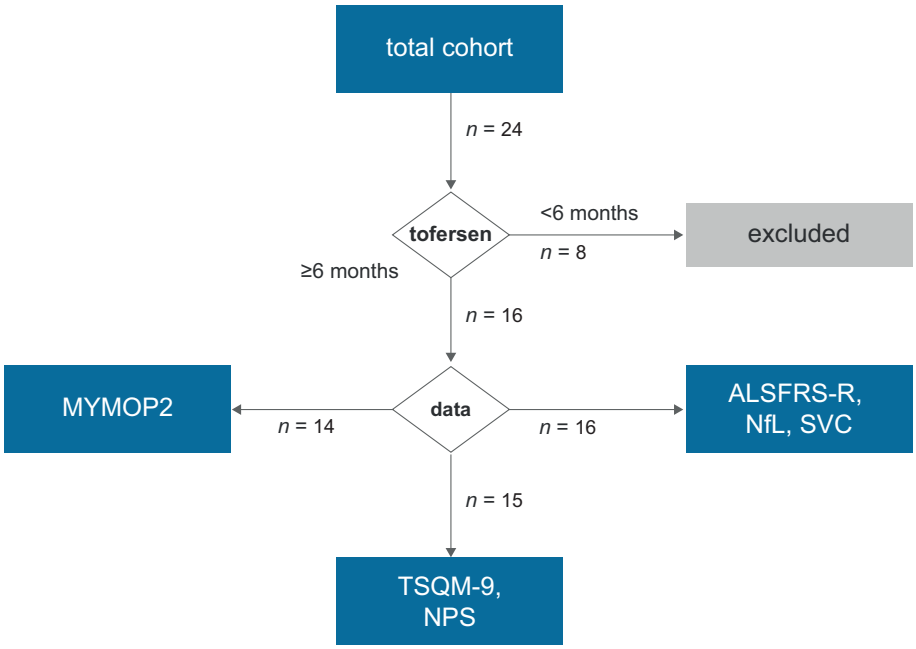


FIGURE 1 Studied cohort of ALS-*SOD1* patients receiving tofersen. A total cohort of ALS patients with *SOD1* mutations (*SOD1*-ALS) receiving tofersen was investigated. Data sets for ALS functional rating scale—revised (ALSFRS-R), neurofilament light chain (NfL), slow vital capacity (SVC), Measure Your Medical Outcome Profile (MYMOP2), Treatment Satisfaction Questionnaire for Medication (TSQM-9), and Net Promoter Score (NPS) were obtained. *n* = number of patients and available datasets, respectively.

TABLE 1 Clinical and genetic characteristics.

Patient	Age	M/F	Disease duration (months)	ALSFRS-R	ALS-PR	ALS-PR classification	Family history	SOD1 mutation	Allele genotype
#1	59	F	42	45	0.1	Slower	Negative	C.272a>c, p.(asp91ala)	Homozygous
#2	49	F	22	42	0.3	Slower	Negative	C.272a>c, p.(asp91Ala)	Homozygous
#3	59	M	33	46	0.1	Slower	Negative	C.272a>c, p.(asp91Ala)	Homozygous
#4	54	M	108	45	0.1	Slower	Positive	C.346c>g, p.(arg116gly)	Heterozygous
#5	59	F	16	35	0.8	Intermediate	Positive	C.346c>g, p.(arg116gly)	Heterozygous
#6	53	F	19	42	0.3	Slower	Negative	C.272a>c, p.(asp91ala)	Heterozygous
#7	55	F	45	37	0.2	Slower	Negative	C.272a>c, p.(asp91ala)	Heterozygous
#8	71	F	53	28	0.4	Slower	Negative	C.272a>c, p.(asp91ala)	Heterozygous
#9	32	M	31	17	1.0	Intermediate	Negative	C.197a>g, p.(asn66ser)	Homozygous
#10	39	F	15	34	0.9	Intermediate	Negative	C.358-10t>g	Heterozygous
#11	52	M	209	27	0.1	Slower	Positive	C.140a>g, p.(his47arg)	Heterozygous
#12	49	F	14	44	0.3	Slower	Positive	C.125g>a, p.(gly42asp)	Heterozygous
#13	61	M	4	42	1.5	Faster	Positive	C.346c>g, p.(arg116gly)	Heterozygous
#14	64	M	22	36	0.6	Intermediate	Positive	C.435g>c, p.(leu145phe)	Heterozygous
#15	50	F	105	25	0.2	Slower	Negative	C.272a>c, p.(asp91ala)	Homozygous
#16	44	M	80	34	0.2	Slower	Negative	C.400_402del, p.(glu134del)	Heterozygous

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS functional rating scale—revised; ALS-PR, ALS progression rate; duration, disease duration; F, female; M, male.

3 | RESULTS

3.1 | Analyzed patient cohort

The analyzed cohort was extracted from a larger cohort of 24 SOD1-ALS that participated in the EAP of tofersen and agreed to data collection. Sixteen SOD1-ALS patients were investigated who received tofersen for at least 6 months and had complete data sets for clinical data, ALSFRS-R and sNfL. Data of SVC, MYMOP2, TSQM-9, and NPS were available for most, but not all participants and visits (Figure 1). Five of 16 patients being studied here, had been included in a prior investigation.[16] One of the patients of the prior

TABLE 2 Clinical course and neurofilament light chain before and during tofersen treatment.

ID #	Treatment duration (months)	ALSFRS-R pre-treatment	ALSFRS-R during treatment	ALSFRS-R change	ALS-PR pre-treatment	ALS-PR during treatment	ALS-PR change	SVC pre-treatment (%)	SVC during treatment (%)	SVC change (%)	sNfL pre-treatment (pg/mL)	sNfL during treatment (pg/mL)	sNfL change
#1	18	45	42	−3	0.1	0.1	0.0	125	128	+3	61.6	19.1	−69%
#2	17	42	43	1	0.3	0.1	−0.2	95	100	+5	107.0	9.3	−91%
#3	17	46	43	−3	0.1	0.1	0.0	85	113	+28	63.3	18.1	−71%
#4	15	45	45	−2	0.1	0.1	0.0	96	95	−1	177.4	38.0	−79%
#5	15	35	32	−3	0.8	0.5	−0.3	103	91	−12	62.3	20.0	−68%
#6	12	42	40	−2	0.3	0.3	0.0	115	123	+8	57.8	73.6	+27%
#7	11	37	40	3	0.2	0.1	−0.1	77	86	+9	50.0	31.2	−38%
#8	11	28	30	2	0.4	0.3	−0.1	149	136	−13	36.7	27.3	−25%
#9	10	17	26	9	1.0	0.5	−0.5	34	46	+12	27.5	5.4	−80%
#10	10	34	29	−5	0.9	0.8	−0.1	92	86	−6	148.0	44.3	−70%
#11	9	27	25	2	0.1	0.1	0.0	n.a	n.a	n.a	12.2	7.8	−36%
#12	8	44	47	3	0.3	0.1	−0.2	n.a	n.a.	n.a.	37.0	8.8	−76%
#13	7	42	43	1	1.5	0.5	−1.1	87	72	−15	21.5	3.9	−82%
#14	6	36	32	−4	0.6	0.6	0.0	45	63	+18	66.5	23.8	−64%
#15	6	25	24	−1	0.2	0.2	0.0	30	28	−2	55.7	23.3	−58%
#16	6	34	34	0	0.2	0.2	0.0	62	69	+7	13.8	7.9	−43%
Mean	11	36	36	0	0.4	0.3	−0.2	85	88	+3	62.0	23.0	−58%
Min	6	17	24	−5	0.1	0.1	−1.1	30	28	−15	12.0	4.0	−91%
Max	18	46	47	9	1.5	0.8	0.0	149	136	+28	177.0	74.0	+27%

Abbreviations: ALSFRS-R, ALS functional rating scale—revised; ALS-PR, ALS progression rate; n.a., not applicable; sNfL, neurofilament light chain in serum; SVC, slow vital capacity in percent of normal.

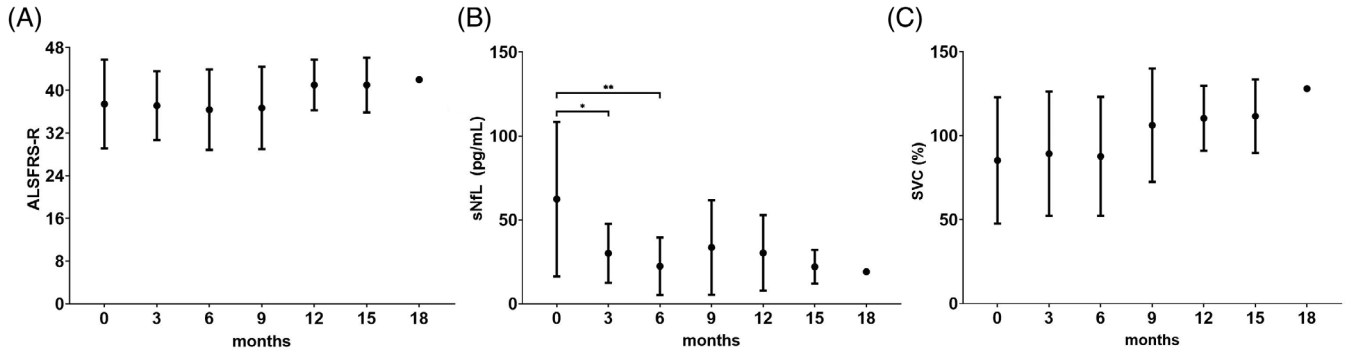


FIGURE 2 ALSFRS-R, sNfL and SVC during treatment with tofersen. (A) ALS functional rating scale—revised (ALSFRS-R), (B) serum neurofilament light chain (sNfL), and (C) slow vital capacity in percent of normal (SVC) during the treatment with tofersen. Tofersen (months), number of months of tofersen treatment. Bar, mean value; hinges, standard deviation. Significance levels: $^{*}p \leq .05$; $^{**}p \leq .01$.

report was lost to follow-up. Seven patients had been included in a prior investigation with shorter observation period and without patient-reported outcomes measures.[17]

3.2 | Clinical and genetic characteristics

The clinical characteristics are summarized in Table 1. Mean age was 53 years (range 32–71 years), disease duration 51 months (range 4–209 months). Ten of these 16 patients reported a negative family history. Patients with eight distinct SOD1 mutations were included. The mutation C.272a>c, p.(asp91ala) was most frequent and found in seven cases (four homozygous and three heterozygous mutations, respectively).

3.3 | Tofersen treatment

The mean tofersen treatment duration was 11 months (range 6–18 months). No subject discontinued treatment due to adverse event or other reasons. None of the patients underwent gastrostomy, non-invasive ventilation, or a tracheotomy with invasive ventilation. Individual treatment duration is shown in Table 2. The drug was very well tolerated. The reported adverse events are summarized in Table S1.

3.4 | ALSFRS-R before and during tofersen treatment

Mean ALSFRS-R before treatment was 36 (range 17–46). During treatment ALSFRS-R increased in seven patients and was unchanged in one individual ($n = 8$, 50%). Data are shown in Table 2, Table S2, Figure 2, and Figure S1.

3.5 | ALS-PR before and during tofersen treatment

ALS-PR before tofersen treatment was slower in 11 patients (minimum 0.1), intermediate in four, and faster in one (1.5). During tofersen treatment, ALS-PR was reduced in eight of the 16 patients (50%) demonstrating a slowing of disease progression. One patient (ID #13) showed a reduction of ALS-PR from 1.5 to 0.5 within 7 months of therapy. ALS-PR was unchanged in the remaining eight participants. There was no patient with an increased ALS-PR during treatment. Data are shown in Table 2, Table S2, Figure 2, and Figure S1.

3.6 | SVC before and during tofersen treatment

Mean SVC before treatment was 85 percent of normal (range 30%–149%). During tofersen treatment, SVC was stable (mean 88%, range −15% to +28%). Data are shown in Table 2, Table S2, Figure 2, and Figure S1.

3.7 | sNfL before and during tofersen treatment

Mean sNfL before treatment was 62 pg/mL (range 12–177 pg/mL). During tofersen treatment, mean NfL decreased to 23 pg/mL (range 4–74 pg/mL, relative reduction −58%). NfL response was found in all patients—except one heterozygous D91A mutation carrier (ID #6) with increase of sNfL by 27%. Repeated measures ANOVA also showed significant results (sNfL $p = .01$). Data are shown in Table 2, Table S2, Figure 2, and Figure S1.

3.8 | MYMOP2

3.8.1 | Prioritized symptoms

Twenty-eight prioritized symptoms (of 14 participants) were captured (Table 3 and Table S3). In ranked order, seven domains were prioritized: walking and motor functions of the lower limbs ($n = 12$), arm or hand functions ($n = 7$), general mobility or autonomy ($n = 3$), breathing ($n = 2$), fasciculations ($n = 2$), cramps ($n = 1$), and pain ($n = 1$).

TABLE 3 Treatment response to tofersen using MYMOP2.

Patient	MYMOP-2	Symptoms	Experience (months)	First perception	Latest perception	Change	Responder status
#1	Symptom 1	Walking	18	6	3	−3	+
	Symptom 2	Pain in legs		3	3	0	
	Activity	Walking		5	3	−2	+
#2	Symptom 1	Walking	17	5	2	−3	+
	Symptom 2	Fasciculations		4	2	−2	
	Activity	Walking		5	2	−3	+
#3	Symptom 1	Muscle cramps	17	3	3	0	+
	Symptom 2	Fasciculations		3	2	−1	
	Activity	Walking		4	3	−1	+
#4	Symptom 1	Weakness of left arm	15	5	5	0	+/−
	Symptom 2	Weakness of right arm		1	5	4	
	Activity	Driving car		4	3	−1	+
#5	Symptom 1	General mobility	15	4	4	0	+/−
	Symptom 2	Autonomy		4	4	0	
	Activity	Walking outside		4	5	1	−
#6	Symptom 1	Walking	12	2	3	1	+/−
	Symptom 2	Weakness of hand		3	3	0	
	Activity	Handcrafting		5	3	−2	+
#7	Symptom 1	Mobility of hands	11	3	3	0	+/−
	Symptom 2	Walking		3	4	1	
	Activity	Walking outside		6	5	−1	+
#8	Symptom 1	Walking	11	4	3	−1	+
	Symptom 2	Function of right hand		4	4	0	
	Activity	Dancing		5	5	0	+/−
#9	Symptom 1	Walking	10	5	6	1	+
	Symptom 2	Breathing		5	4	−1	
	Activity	Gaming		6	2	−4	+
#10	Symptom 1	Weakness of right arm	8	5	4	−1	+
	Symptom 2	Weakness of right leg		3	3	0	
	Activity	Walking		3	3	0	+/−
#13	Symptom 1	Walking	7	4	2	−2	+
	Symptom 2	Spasticity in legs		4	3	−1	
	Activity	Being outside		6	3	−3	+
#14	Symptom 1	Dyspnea	6	3	3	0	+
	Symptom 2	General weakness		5	4	−1	
	Activity	No data available		4	3	−1	+
#15	Symptom 1	Weakness of legs	7	5	1	−4	+
	Symptom 2	Extension of fingers		3	3	0	
	Activity	Meeting friends		3	3	0	+/−
#16	Symptom 1	Fasciculations	6	6	4	−2	+
	Symptom 2	Mobility of legs		3	3	0	
	Activity	Use of computer		0	4	4	−

Note: Experience: number of months with tofersen treatment; First perception: MYMOP rating before tofersen treatment; Last perception: MYMOP rating at the latest time during tofersen therapy; Change: difference between first and last perception (Likert scale points); Responder status: (+) responder, (+/−) partial responder, (−) non-responder.

Abbreviation: MYMOP2, Measure Yourself Medical Outcome Profile (MYMOP2).

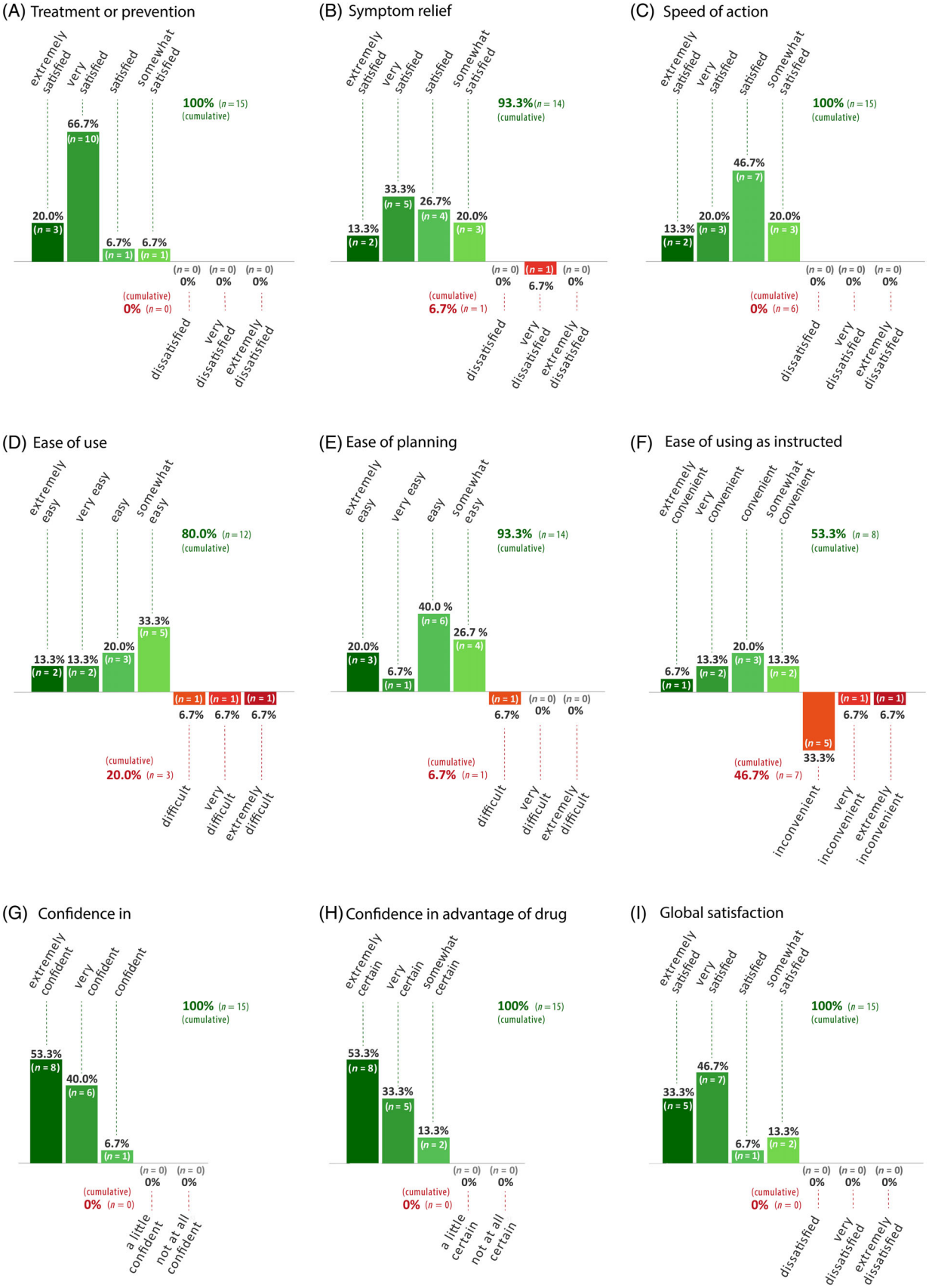


FIGURE 3 Treatment satisfaction with tofersen as assessed by Treatment Satisfaction Questionnaire for Medication (TSQM-9). Depiction of results of the nine TQSM-9 questions. *n* = number of patients.

3.8.2 | Response to treatment

Ten of 14 participants (71%) perceived an improvement in at least one of the two target symptoms being "responders" to tofersen therapy. Two individuals (14%) reported an improvement in both prioritized symptoms. Four patients (29%) were allocated to the group of "partial responder." No patient perceived deterioration in both prioritized symptoms and was classified as "non-responder" (Table 2).

3.8.3 | Perception of treatment

At baseline, the mean symptom severity—as assessed on the MYMOP2/7-point Likert scale was 3.8 ($n = 14$). During follow-up of tofersen therapy, a reduced mean symptom severity of 3.0 points was identified (18% relative reduction, Table S3).

3.8.4 | Treatment satisfaction measured by TSQM-9

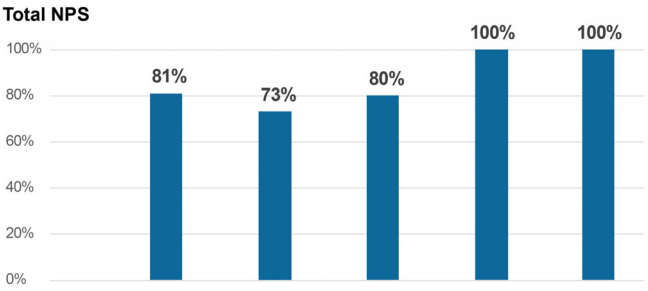
Patient treatment satisfaction with tofersen, as assessed by TSQM-9, is shown in Figure 3 and Figure S2. The question "How satisfied or dissatisfied are you with the ability of tofersen to prevent or treat ALS?" received the highest score of all the 9 TSQM-related questions, followed by the question concerning the "overall satisfaction." In contrast, the questions about the usability and convenience of the drug were rated more critically (Figure 3 and Figure S2).

3.8.5 | Treatment recommendation measured by NPS

At 6 months of tofersen treatment, 12 of 15 patients (80%) were "promoters" of tofersen. The remaining three patients were "passives." There were no "detractors." The NPS total score—the difference between the percentage of "promoters" and "detractors" was +80. During treatment the NPS increased to 100% at nine ($n = 9$) and 12 months ($n = 6$), respectively (Figure 4).

4 | DISCUSSION

In this study, tofersen therapy was investigated in a wide spectrum of *SOD1*-ALS patients in terms of age, duration of disease and functional deficits. NfL data correspond with the VALOR study results and underscore the role of NfL as an early treatment response marker in ALS. Furthermore, the presented data support the positive outcome as measured by ALSFRS-R and ALS-PR, the established clinical endpoints in ALS. PROs showed a favorable perception of tofersen therapy in most patients and added initial self-reported data on treatment experience.



Tofersen	1 month	3 months	6 months	9 months	12 months
n = patients	16	15	15	9	6
Promoters	13	11	12	9	6
Passives	3	4	3	0	0
Detractors	0	0	0	0	0
NPS	**81%**	**73%**	**80%**	**100%**	**100%**

FIGURE 4 Recommendation of tofersen using the Net Promoter Score (NPS) relative to the duration of therapy. The NPS shows the percentage of patients who are promoters subtracted by the percentage of patients who are detractors.

4.1 | Clinical and genetic characteristics

Half of the patients reported a negative family history emphasizing the importance of genetic screening for *SOD1* mutations in apparently sporadic ALS—independent of the patient's age.[36–38] Mean and maximum disease duration at the beginning of tofersen were higher than in the VALOR study (51 and 209 months vs. 11 and 29 months, respectively) suggesting clinical differences of the trial and clinical practice cohorts.

4.2 | ALSFRS-R and ALS progression before and during tofersen treatment

ALS progression at baseline was substantially lower in this clinical practice cohort as compared to the phase 3 trial.[5] One reason was that a high proportion of patients with a D91A mutations were included that are usually associated with slower progressing ALS. The D91A patients also represent a limitation because heterozygous D91A mutations may have incomplete penetrance or can even be considered a carrier status.[39–41] The inherently slow progression in D91A patients and the relatively short duration of the observation period make it difficult to conclusively interpret the data in the D91A patients. However, five patients with intermediate or faster progressing ALS were suitable to recognize a response to therapy. These patients showed the beginning of a stabilization or even improvement at 4–6 weeks of treatment (Table S2). In the total cohort, mean relative reduction of ALS progression was 25%. Remarkably, one individual (ID #9) improved by nine ALSFRS-R points. Given the baseline of impairment and the extent of the improvement, a placebo effect is less likely. Based on this assumption, it is conceivable that—in yet ill-defined preconditions—tofersen has the potential to rescue motor functions and to partially reverse functional deficits in *SOD1*-ALS.

4.3 | sNfL before and during tofersen treatment

Mean sNfL before treatment was similar to that of a large multicenter NfL study.[8] During tofersen treatment, mean NfL decreased by 58%—a biomarker response to tofersen that reproduced the VALOR and OLE study and extended our previous report.[16,17] NfL response was found in all patients—except one heterozygous D91A mutation carrier (ID #6) showing an increase of sNfL. However, two other heterozygous D91A carriers (#7 and #8) revealed a modest NfL decline (Table 2). The causes of the differential sNfL response in this mutation and other *SOD1* variants await further clarification. Overall, the finding of rapid and strong sNfL response underscores the feasibility of NfL as a therapeutic biomarker in an expanded clinical spectrum of *SOD1*-ALS.[5,16,17]

4.4 | Treatment expectations measured by MYMOP2

Limb functions, mainly of the lower extremities, dominated as "target" symptoms of tofersen treatment. Only two patients prioritized respiratory functions. No patient mentioned bulbar symptoms. This profile of prioritized symptoms might reflect some bias of the studied cohort for more slowly progressive ALS with less involvement of the bulbar and respiratory domains. When referencing the symptoms to ALSFRS-R items, a first and second order reference can be differentiated. In this definition, the prioritized symptom refers literarily (first order) or implicitly (second order) to distinct items of the ALSFRS-R. However, only 32% and 42% of symptoms showed a first or second order reference, respectively. Twenty-five percent of symptoms were not reflected in the ALSFRS-R (Table S3). This finding underscores that not all symptoms and impairments—and treatment goals—a covered by the ALSFRS-R. It contributes to the notion that PROs are important components to measure outcomes in ALS.

4.5 | Response to treatment measured by MYMOP

Self-rating of the MYMOP Likert scale showed a relative reduction of prioritized symptoms similar to the reduction of ALS-PR. More patients responded positively to tofersen using MYMOP2 as compared to ALSFRS-R (50%). This finding may reflect the wider coverage of individual symptoms using MYMOP2 and may indicate an increased sensitivity to minor changes that is not captured by the rather gross grading of ALSFRS-R. However, this conclusion must be viewed with caution as the definition of responder, partial responder and non-responder were set for the purpose of this study. Further comparative and long-term studies are needed to investigate the consistency and meaningfulness in the change of MYMOP2 self-rating.

4.6 | Treatment satisfaction measured by TSQM-9

Most patients gave a positive rating ("extremely satisfied" to "satisfied") to the question about the ability of tofersen to "prevent or treat" ALS. Only the domain of "convenience" was rated more critically. Although the reasons for the patient dissatisfaction were not assessed, the intrathecal administration and the frequency of tofersen therapy might cause the lower rating. However, the summarizing question on "global satisfaction" was very positively rated indicating that the burden of therapy was outweighed by the benefit of treatment.

4.7 | Treatment recommendation measured by NPS

The NPS serves as a robust instrument for the assessment of products and services.[35] Although the validation of this score in medicine is still limited, the NPS is finding growing use in outcome research.[42–44] In this study, the NPS score showed a very positive patient recommendation of tofersen and higher ratings with longer therapy. However, caution is warranted when transferring the NPS system—being optimized for validating consumer products and services—to medical treatment options. The positive NPS results were remarkable as not all patients reported a stabilization or even improvements during treatment. However, the psychosocial dimension of PROs was beyond the scope of this study and needs further research.

In conclusion, this clinical practice cohort added more data on clinical and patient-reported outcomes and neurofilament response during tofersen treatment in *SOD1*-related ALS. Notwithstanding the overall positive outcome in this observation, the generalizability of this study is limited due to the open label design, restricted patient population, and rather small spectrum of *SOD1* mutations. Further research is needed to better understand the individual differences of clinical and NfL treatment response, and the extent to which tofersen can modify the course of disease during long-term treatment.

AUTHOR CONTRIBUTIONS

Thomas Meyer: Conceptualization; methodology; data curation; supervision; resources; project administration; formal analysis; validation; visualization; writing – original draft; funding acquisition; investigation; writing – review and editing. **Peggy Schumann:** Investigation; writing – review and editing; visualization; validation; methodology; project administration; data curation; conceptualization; formal analysis. **Patrick Weydt:** Investigation; writing – review and editing; validation; resources. **Susanne Petri:** Investigation; writing – review and editing; validation; resources; project administration. **Jochen H. Weishaupt:** Conceptualization; investigation; writing – review and editing; formal analysis; data curation; supervision; resources; project administration. **Ute Weyen:** Investigation; writing – review and editing; validation; resources; project administration. **Jan C. Koch:** Investigation; writing – review and editing; resources; project administration.

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CONFLICT OF INTEREST STATEMENT

TM is on the advisory board of Biogen and has received consulting fees from Biogen. PK received consulting fees from Biogen. RG has received grants, personal fees, non-financial support and research support from Biogen and serving on the advisory board of Biogen, outside of the submitted work. SP has participated in advisory boards of Biogen and has received consulting fees from Biogen. TM and CM are founders and shareholders of the Ambulanzpartner Soziotechnologie APST GmbH, which makes the internet platform Ambulanzpartner and the mobile application "ALS-App." APST received a research grant from Biogen.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

We, the authors, confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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