23 February 2024
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EMADOC-1700519818-1297967
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Qalsody (tofersen)
Treatment of amyotrophic lateral sclerosis
EU/3/16/1732

Sponsor: Biogen Netherlands B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	Synthetic ribonucleic acid oligonucleotide directed against superoxide dismutase 1 messenger ribonucleic acid
Other name(s)	-
International Non-Proprietary Name	Tofersen
Tradename	Qalsody
Orphan condition	Treatment of amyotrophic lateral sclerosis
Sponsor's details:	Biogen Netherlands B.V. Prins Mauritslaan 13 1171 LP Badhoevedorp Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Biogen Idec Limited
COMP opinion	13 July 2016
EC decision	29 August 2016
EC registration number	EU/3/16/1732
Post-designation procedural history	
Transfer of sponsorship	Transfer from Biogen Idec Limited to Biogen Netherlands B.V. – EC decision of 8 May 2019
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Martina Weise / Alexandre Moreau
Applicant	Biogen Netherlands B.V.
Application submission	30 October 2022
Procedure start	1 December 2022
Procedure number	EMA/H/C/0005493
Invented name	Qalsody
Proposed therapeutic indication	Qalsody is indicated for the treatment of adults with amyotrophic lateral sclerosis (ALS), associated with a mutation in the superoxide dismutase 1 (SOD1) gene. Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Qalsody
CHMP opinion	22 February 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Darius Matusevicius / Robert Nistico
Sponsor's report submission	18 August 2023
COMP opinion (adoption via written procedure)	23 February 2024

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2016 designation was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing synthetic ribonucleic acid oligonucleotide directed against superoxide dismutase 1 messenger ribonucleic acid was considered justified based on improvements in motor function and survival upon treatment in a valid preclinical model of the condition;
- the condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure. The survival of the patients is usually limited to 2-3 years;
- the condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing synthetic ribonucleic acid oligonucleotide directed against superoxide dismutase 1 messenger ribonucleic acid will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data which demonstrate that treatment improved motor function. The currently authorised product does not have a therapeutic effect on motor function. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the degeneration of both upper motor neurons (UMNs) and lower motor neurons (LMNs), leading to muscle weakness, spasticity, dysphagia, and paralysis. Unable to function, the muscles weaken and become atrophic. The loss of motor neurons leads to progressive loss of muscle mass, strength, and function in bulbar, respiratory, and limb muscles, typically leading to paralysis and ultimately death from respiratory

failure. ALS may present in any anatomical region and spread throughout the body with variable speeds and patterns in different patients. In the general ALS population mean age at onset occurs at around 61.1 ± 12 years [Opie Martin 2022].

The pathogenesis of ALS is not completely understood. In most patients ALS arises sporadically (sALS), and the cause is unknown (Hardiman et al. 2017). Approximately 10% of ALS is familial (fALS) and caused by an autosomal dominant mutation. The most frequent mutation leading to fALS is a hexanucleotide G4C2 repeat expansion in the C9ORF72 gene (leading to aggregating dipeptide-repeat proteins), accounting for about 30% to 40% of fALS and up to 8% of sALS (Hardiman et al. 2017). Mutations in the gene encoding the enzyme Cu/Zn superoxide dismutase (*SOD1)* are the second-most common cause of fALS, found in about 10-20% of cases, as well as 1-2% of sALS cases. Mutations in the SOD1 gene cause a build-up of a toxic form of the SOD1 protein. This causes destruction of motor neurons, leading to weakness and wasting of muscl tissue. The natural history of SOD1-ALS is highly variable (>200 different SOD1 mutations known to date) but usually occurs earlier than in the general ALS population with a mean onset of 49.7 ± 12.3 years. SOD1-ALS is associated with a LMN predominant phenotype and is rarely associated with cognitive impairment (Li 2016).

The approved therapeutic indication "*Qalsody is indicated for the treatment of adults with amyotrophic lateral sclerosis (ALS), associated with a mutation in the superoxide dismutase 1 (SOD1) gene"* falls within the scope of the designated orphan condition "treatment of amyotrophic lateral sclerosis".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

ALS is considered to be a chronically debilitating and life-threatening condition.

Individuals affected by the disorder gradually lose their ability to initiate and control voluntary movement. This progressive paralysis leads to the patient's inability to carry out activities of daily living, such as walking, writing, talking, eating etc. ALS tends to progress quickly over months, leading to severe disability and loss of physical independence within one to two years. Up to 50% of patients develop non-motor symptoms, including cognitive and/or behavioural impairment.

Usually in the late stages of the disease, respiratory insufficiency emerges due to the weakening and paralysis of the muscles involved in respiratory function, such as the upper airway muscles, the pharyngeal and laryngeal muscles, and most prominently, the diaphragm (de Carvalho et al, 2019). The progressive loss of motor neurons typically leading to paralysis and ultimately death from respiratory failure.

Median survival from symptom onset is only 2–4 years [Feldman 2022; Brown 2017], with median duration of 2.93 years recently reported in a large (n=12,622) ALS cohort. However, there is a broad distribution of individual patient survival. This variability is attributable to various factors that influence survival, such as clinical and demographic features (e.g., age at onset, site of onset, and presence of frontotemporal dementia), genetic architecture (e.g., rapidly progressive SOD1 A5V and slowly progressive DCTN1 mutations), and the exposome (e.g., environmental exposures). The ENCALS model was created to predict personalised survival (defined as survival without tracheostomy or non-invasive ventilation >23 h/day) based on eight parameters: onset age, time to diagnosis, ALSFRS-R progression rate, forced vital capacity, bulbar onset, definite ALS by revised El Escorial criteria, frontotemporal dementia, and C9orf72 repeat expansion (Figure 6) [Westeneng 2018]. Five

distinct survival groups are defined with median survivals ranging from very short (predicted median survival 17·7 months) to very long (predicted median survival 91·0 months). This model notwithstanding, accurate prognostication of the clinical course of the disease remains in its infancy since even predictions by the best models retain uncertainty [Feldman 2022].

Most patients with SOD1 mutations develop a rapidly progressive ALS, although some cases show a diverse phenotype. Age at onset and severity may vary significantly depending on the variants involved. The most current and comprehensive overviews stem from a retrospective cohort study that reviewed records from 175 SOD1-ALS patients across 15 institutions in North America [Bali 2017] and a more recently reported SOD1-ALS dataset comprising of 1383 individuals [Opie Martin 2022]. Mean age of onset was 49.7 ± 12.3 years in the smaller study and 48.9 ± 12.8 years in the larger dataset. The larger study also included a comparator dataset comprising of 12,622 ALS patients constructed from individual population-based datasets of ALS in five European populations (UK, Netherlands, Italy, Ireland and Belgium) and the United States (STRENGTH cohort). In the general ALS population mean age at onset occurs considerably late in life at 61.1 ± 12 years [Opie Martin 2022].

Number of people affected or at risk

At the time of Orphan designation in 2016, the prevalence was calculated at 9.99 per 100,000 for the EEA and 9.95 per 100,000 for the then 28 countries in the EU and agreed to be 1 in 10,000 by the COMP. The sponsor now proposes an estimated prevalence for ALS in the EU/EEA of 0.655 per 10,000 persons.

This estimate is based on 17 studies from 6 EU/EEA countries directly reporting prevalence data (Table 1). The Sponsor chose this direct prevalence estimation approach instead of an indirect estimation approach from incidence and survival rates as it was considered more reliable.

The regional pooled prevalence estimate for Europe was 6.55 (95%CI: 5.49, 7.82) per 100,000 population. Using the total EU27, Norway, Iceland, and Liechtenstein population of 452,576,117 in 2023 from Eurostat, the expected number of prevalent ALS cases can be calculated as: (6.55 x 452,576,117)/100,000 = 29,644 (rounded to nearest integer).

The sponsor recognises that this prevalence estimate is only approximately half the rate that has been accepted by the COMP in the most recent ALS orphan designation procedures which ranged from 1 to 1.3 per 10,000 persons. These estimates are higher than most reported prevalence estimates in the literature. Nevertheless, the sponsor notes that if the most conservative approach to estimating the prevalence of ALS in the EU/EEA is preferred, then applying the highest reported prevalence rate from a single study (12.26 per 100,000 from [Chiò 2017]), the estimated number of prevalent ALS cases would be 55,486 individuals living with ALS in the EU/EEA.

Table 1. Studies reporting prevalence rates of ALS in Europe

	Studies reporting prevalence of ALS	
Country	**Author, year**	**Prevalence rate per 100,000 population**
Belgium	Roy 2015	3.20
	median (range)	**3.2 (NA)**
Ireland	Lefter 2017	7.20
	O'Toole 2008	6.40
	Traynor 1999	4.70
	median (range)	**6.40 (4.70, 7.20)**
Italy	Chiò 2017	12.26
	Palese 2019	7.97
	Scialò 2016	7.85
	Pugliatti 2013	10.80
	Mandrioli 2003	4.63
	Drigo 2013	5.27
	Chiò 2009a	7.89
	median (range)	**7.89 (4.63–12.26)**
Netherlands	Huisman 2011	8.51
	median (range)	**8.51 (NA)**
Norway	Benjaminsen 2018	3.69
	Gundersen 2011	4.05
	Nakken 2018	7.63
	median (range)	**4.05 (3.69–7.63)**
Spain	Pradas 2013	5.40
	Aragones 2016	8.38
	median (range)	**6.89 (5.40–8.38)**
Total	**median (range)**	**6.55 (95%CI: 5.49, 7.82)**
Total	**mean (range)**	**6.81 (3.20, 12.26)**

The COMP acknowledged that previously adopted prevalence estimates are rather conservative and possibly more reflective of a worst-case prevalence estimation. This may in part be owing to different methodologies used to calculate the prevalence such as indirect approaches based on incidence and disease duration vs direct approaches based on reported prevalence data. Furthermore, some methodologies also imputed data from countries where prevalence was reported to be highest to countries where no epidemiologic data for ALS was available.

The COMP considered that an up-rounded prevalence estimate of approximately 0.7 per 10,000 is acceptable and more reflective of an average value for this condition in the EU/EEA (total ALS population). Using the total EU27, Norway, Iceland, and Liechtenstein population of 452,576,117 in 2023 from Eurostat, the expected number of prevalent ALS cases can be calculated as: (0.7 x 452,576,117)/10,000 = 31,680 persons.

Of note, an estimated 2% of the ALS disease is attributed to mutations in the superoxide dismutase 1 (*SOD1*) gene (SOD1-ALS). According to the above prevalence estimate for the total ALS population, the

figure for SOD1-ALS in the EU/EEA is approximately 0.014 per 10,000 which equals around 444 SOD1-ALS patients in the EU/EEA.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The only currently authorized drug for the treatment of ALS in the EU is Riluzole (Rilutek). This product is considered the current standard of care in ALS in the EU. It was approved for use in ALS in 1996 and is a glutamate receptor antagonist (Oskarsson et al, 2018).

The therapeutic indication as per 4.1 of the SmPC reads as follows:

> "*RILUTEK is indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS). Clinical trials have demonstrated that RILUTEK extends survival for patients with ALS (see section 5.1).*
>
> *Survival was defined as patients who were alive, not intubated for mechanical ventilation and tracheotomy-free. There is no evidence that RILUTEK exerts a therapeutic effect on motor function, lung function, fasciculations, muscle strength and motor symptoms.*
>
> *RILUTEK has not been shown to be effective in the late stages of ALS. Safety and efficacy of RILUTEK has only been studied in ALS. Therefore, RILUTEK should not be used in patients with any other form of motor neurone disease."*

Several studies have shown that Riluzole prolongs survival by 3-6 months (van Es et al, 2017). However, Riluzole has not been shown to slow neurodegeneration and decline in motor function in ALS patients (Hobson et al., 2016).

The sponsor argues that riluzole is not a satisfactory method of treatment of ALS with respect to any of the debilitating functional manifestations of the condition, including motor and lung function decline, fasciculations, loss of muscle strength, and motor symptoms. While it is agreed that Qalsody may improve different aspects of the disease in ALS-SOD1 patients, riluzole still remains a cornerstone of therapy in all ALS patients, including those with SOD1 mutations. Also, the therapeutic indication wording of Qalsody does not determine its clinical positioning vs riluzole. In the pivotal clinical study of Qalsody more than 60% of patients included in the study received background treatment with riluzole. The therapeutic indication wording suggests that Qalsody can be administered as monotherapy and in combination with riluzole, in line with the data from the pivotal study.

Of note, the sponsor mentions the plans of the European Academy of Neurology (EAN) to update their clinical ALS guideline (van Damme et al., 2023 EAN congress July 2023). In there, tofersen might be recommended as 1st line treatment option in ALS-SOD1 patients.

In conclusion, riluzole is considered a satisfactory method for the purpose of determining the significant benefit in the orphan maintenance procedure of Qalsody.

Significant benefit

The sponsor claims that tofersen (with or without concomitant riluzole) represents a clinically relevant advantage (CRA) over riluzole in terms of improved efficacy, i.e. improved survival (death equivalent and overall), and efficacy on clinical function endpoints.

In support of their claims, the sponsor presents data from their pivotal randomized, placebo controlled 28-week Phase 3 study (Study 101 Part C, VALOR) and integrated analyses from Study 101 and interim analyses of the open-label extension study 102 with follow-up data up to 104 weeks (latest data cut 28 February 2023). Of note, the data from the VALOR study and integrated analyses including interim data from study 102 up to 52 weeks have been published by Miller and colleagues in 2022 (*N Engl J Med. 2022 Sep 22;387(12):1099-1110. doi: 10.1056/NEJMoa2204705*). The COMP noted that the pivotal VALOR study failed to demonstrate a statistically significant effect in the pre-specified primary analysis of the primary endpoint (predefined ALSFRS-R change to week 28) as well as in the post-hoc analysis of the primary endpoint at the 28-week timepoint which adjusted for imbalances in a possible prognostic biomarker (NfL). Nevertheless, follow-up data to week 104 showed that primary and secondary endpoints were consistently in favour of tofersen.

In view of the above, the COMP considered that a quantitative indirect comparison of survival data of Qalsody vs riluzole is particularly challenging due to the lack of confirmatory evidence with Qalsody at week 28 (number of events observed was too limited) and the difficulty to interpret the post-hoc analyses of pooled data across study 101 and its open-label extension (OLE) study 102. Therefore, the COMP focused mainly on the comparative efficacy on clinical function endpoints of Qalsody vs riluzole (acknowledging that riluzole has no relevant effects on clinical function endpoints).

In particular, the COMP assessed the data from the established ALS Functional Rating Scale–Revised (ALSFRS-R) score and on slow vital capacity (SVC) data. The ALSFRS-R is an established severity score used to assess motor function impairment and decline in ALS patients. The scale consists of 12 items that evaluate different aspects of daily activities grouped into four categories (Bulbar Function, Fine Motor Function, Gross Motor Function, Respiratory Function). Each item is rated on a scale of 0 to 4, thus generating an ALSFRS-R total of score of 0 (maximum disability) to 48 (no disability). Furthermore, change in SVC has been shown to be predictive of respiratory failure, tracheostomy, or death in patients with ALS. A slowing in the rate of SVC decline by 1.5 percent predicted per month was shown to reduce the risk in first onset of respiratory insufficiency or death, first occurrence of tracheostomy or death, and death at any time after 6 months by 22%, 23%, and 23%, respectively ($p < 0.001$) [Andrews 2018]. In addition, the COMP considered the data on the handheld dynamometry (HHD) megascore which is a measure of muscle strength. The HHD megascore was calculated by averaging Z-scores for 16 individual muscle groups in the upper and lower extremities (left and right shoulder flexion, elbow flexion, wrist extension, index finger abduction, thumb abduction, 5th digit abduction, knee extension, and ankle dorsiflexion). Loss of muscle strength is a hallmark of ALS and is relentlessly progressive; increases in strength are not consistent with the natural history of the disease [Cudkowicz 2013; Shefner 2016; Thakore 2021]. The sponsors' separate sub-analyses on the primary and secondary endpoints with tofersen + riluzole over riluzole monotherapy were also considered by the COMP. In addition, the COMP took note of the strong mechanistic basis of tofersen for the treatment of SOD1-ALS, linked to the specific targeted action of the drug.

Of note, the sponsor previously requested protocol assistance on tofersen (EMEA/H/SA/4090/1/2019/PA/III) which included a question on the proposed approach to demonstrate significant benefit. Amongst other aspects, the Sponsor was advised to extend the duration of their pivotal study 233AS101. This advice was not followed, and the study duration was shorter than that recommended in the Agency's advice. The limited study duration may have been a major contributing

factor as to why the pivotal study failed to demonstrate a statistically significant effect (Miller et al., 2022, *N Engl J Med 2022; 387:1099-1110*).

As mentioned above, data from 2 studies, Study 101 Part C and its OLE Study 102, are relied upon to demonstrate the significant benefit of tofersen with or without riluzole over riluzole monotherapy (see below study overview in Table 2, baseline disease characteristics of patients included in study 101 Part C in Table 3 and study schematic as per Figure 1).

Table 2. Clinical studies in patients with SOD1-ALS with tofersen supporting orphan maintenance

Study ID **Phase** **Status**	**Study Design**	**Primary Objective**	**Number of Participants Enrolled**
Study 101 (Part C; VALOR study)			
Phase 3 (pivotal) Complete	Randomized, double-blind, placebo-controlled 28-week study in participants with SOD1-ALS.	Efficacy: Change in ALSFRS-R score to week 28	Tofersen: 72 Placebo: 36
Study 102			
Phase 3 Ongoing	Open-label[a] extension for participants who completed Study 101.	Long-term safety and tolerability	Tofersen: 139[b]

a A blinded loading dose period was incorporated in Study 102 for participants who enrolled after completing Part C of Study 101; blinded placebo or tofersen was administered at Day 15 for those who received tofersen or placebo in Study 101 Part C, respectively. b The 139 participants enrolled includes participants from Part A, B, and C of Study 101. Of these, 95 participants enrolled from Part C of Study 101 into Study 102.

Table 3. Baseline disease characteristics in study 101 Part C (amended from sponsor Table 5)

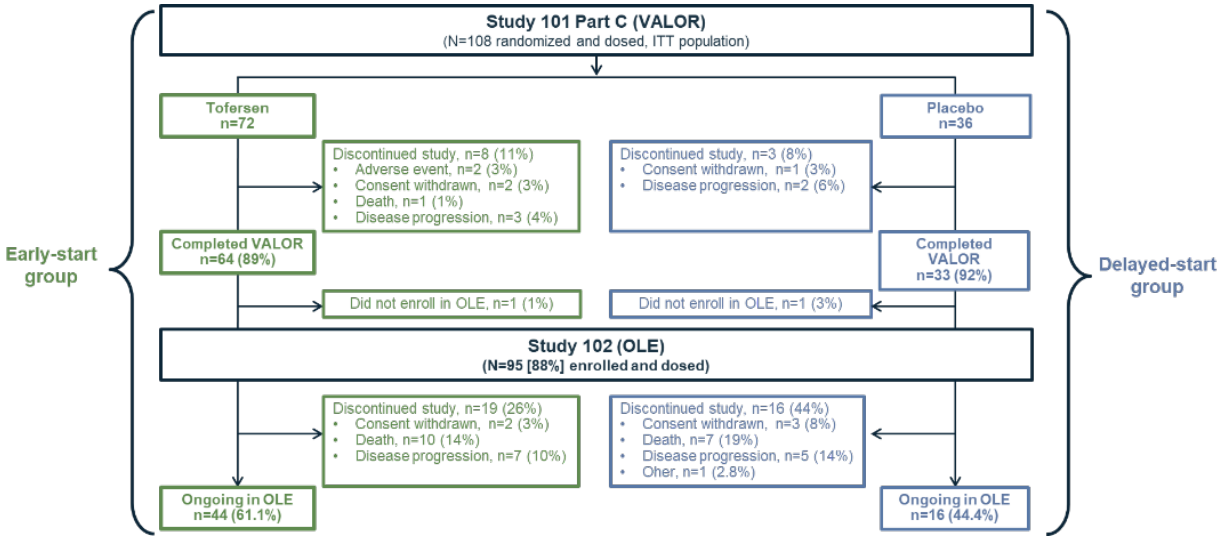
	mITT (n=60)		**non-mITT (n=48)**		**ITT (n=108)**	
	placebo (n=21)	**tofersen 100 mg (n=39)**	**placebo (n=15)**	**tofersen 100 mg (n=33)**	**placebo (n=36)**	**tofersen 100 mg (n=72)**
Mutation[1] type n (%)						
p.Ile114Thr	6 (**29**)	5 (**13**)	4 (27)	5 (15)	10 (**28**)	10 (**14**)
p.Ala5Val	6 (29)	11 (28)	0	0	6 (**17**)	11 (**15**)
p.Gly94Cys	1 (5)	1 (3)	1 (7)	3 (9)	2 (6)	4 (6)
p.His47Arg	0	0	4 (27)	1 (3)	4 (11)	1 (4)
Site of onset n (%)						
Bulbar	2 (10)	3 (8)	1 (7)	0	3 (8)	3 (4)
Lower limbs	14 (67)	19 (49)	12 (80)	27 (82)	26 (72)	46 (64)
Upper limbs	5 (24)	14 (36)	2 (13)	6 (18)	7 (19)	20 (28)
Respiratory	0	1 (3)	0	0	0	1 (1)
Multiple sites	0	2 (5)	0	0	0	2 (3)
Time from symptom onset (months) median (min, max)	**8.3** (2.4, 21.3)	**8.3** (1.7, 18.5)	**39.6** (11.8, 103.2)	**35.5** (3.9, 145.7)	**14.6** (2.4, 103.2)	**11.4** (1.7, 145.7)
ALSFRS-R pre-randomization slope: median (min, max)	**-1.51** (-4.91, -0.42)	**-1.34** (-8.30, -0.39)	**-0.17** (-0.84, -0.02)	**-0.30** (-0.77, 0.00)	**-0.89** (-4.91, -0.02)	**-0.75** (-8.30, 0.00)

	mITT (n=60)		non-mITT (n=48)		ITT (n=108)	
	placebo (n=21)	**tofersen 100 mg (n=39)**	**placebo (n=15)**	**tofersen 100 mg (n=33)**	**placebo (n=36)**	**tofersen 100 mg (n=72)**
ALSFRS-R baseline total score: mean (SD)	**35.4** (5.66)	**36.0** (6.40)	**39.9** (5.09)	**38.1** (5.13)	**37.3** (5.81)	**36.9** (5.91)
Range: min, max	24, 45	15, 44	32, 47	26, 48	24, 47	15, 48
ALSFRS-R run-in slope (Screening to Day 15) raw mean (SD)	-1.3 (3.91)	-1.8 (2.47)	0.1 (1.87)	-0.1 (1.34)	-0.7 (3.25)	-1.0 (2.19)
% predicted SVC at baseline: mean (SD)	83.7 (17.87)	80.3 (14.22)	87.1 (14.82)	84.2 (19.02)	**85.13** (16.53)	**82.1** (16.59)
Range: min, max	57.4, 120.4	46.7, 114.8	54.8, 114.4	55.4, 134.7	54.8, 120.4	46.7, 134.7
Plasma NfL at baseline (pg/mL) mean (SD)	**127.3** (94.4)	**146.2** (82.6)	**37** (29.5)	**47.6** (41.8)	**89.7** (86.5)	**100.4** (82.8)
Geometric mean	92.7	121.8	28.4	33.2	56.6	66.6
Range: min, max	9, 370	12, 329	8, 99	5, 211	8, 370	5, 329

1 Most common mutations, i.e., n > 4

Those participants who were randomised to tofersen in Study 101 are referred to as the 'early-start group', whilst those participants who were originally randomised to placebo and had the opportunity to receive tofersen on entry to Study 102 are referred to as the 'delayed-start group'. The relationships between these groups as they progressed through the 2 studies are shown in Figure 1.

Figure 1. Flow of participants from Study 101 Part C to Week 104 in Study 102



Sources: 2.5, Clinical Overview, Figure 10; 2.7.3, ISE Addendum Appendix 2.1, Output 1

Note: At the time of the 28 February 2023 interim data cut, for the pooled CL group, 16 participants (44.4%) in the placebo/delayed-start group and 44 participants (61.1%) in the early-start group remained ongoing in Study 102.

First the efficacy data on the clinical function endpoints from the pivotal study 101 Part C (28-week data) are described as per the pre-specified primary analysis and as per post-hoc analyses adjusting for baseline plasma neurofilament light chain (NfL) and second the results from the integrated post-hoc analyses of pooled data across study 101 and its open-label extension study 102 (52- and 104-week data). As regards the pooled data, also the sub-analyses by concomitant riluzole use are described for the ALSFRS-R endpoint. The data on the responder analyses of the functional endpoints, the survival data and the data on the pharmacodynamic biomarkers are only summarized briefly.

With regards to the pivotal randomized, double-blind, placebo controlled 28-week study 101 Part C, 108 participants were randomised 2:1 to receive treatment with either tofersen 100 mg or placebo. The predefined primary endpoint was change from baseline to Week 28 in ALSFRS-R score. Key secondary endpoints in order of hierarchical testing included total CSF SOD1 protein, plasma neurofilament light chain, percent-predicted SVC, HHD megascore, time to death or permanent ventilation (PV), and time to death.

Participants included in the study were aged 23 to 78 years with weakness attributable to ALS and a SOD1 mutation. Baseline demographic and most disease characteristics were balanced across treatment arms for use of riluzole and/or edaravone. Approximately 62% of participants were receiving riluzole and 8% were receiving edaravone at baseline, with use balanced across arms. Furthermore, baseline characteristics related to the stage of disease, including time from onset, total ALSFRS-R score, and SVC were balanced across treatment arms. However, baseline neurofilament light chain (NfL) levels, considered to be a likely prognostic biomarker for disease progression by the sponsor, were approximately 15% to 25% higher in the tofersen group than the placebo group, suggesting a possibly faster disease progression in patients in the tofersen group.

The prespecified primary analysis population, or modified intent to treat (mITT) population, comprised the subset (n = 60) of participants who met the prognostic enrichment criteria for rapid disease progression (FPS) based on their SOD1 mutation type and pre-randomization ALSFRS-R slope (≥ 0.2 points/month). All other participants (n = 48) were classified as the non-mITT population and only descriptive analyses were performed. In addition, the sponsor performed several post hoc analyses in the overall ITT population, adjusting for baseline NfL as a covariate. Based on the postulation that NfL has a prognostic value, subgrouping the population according to baseline plasma NfL (≥ median, < median) is expected to minimize these imbalances. The COMP considers NfL as a reliable biomarker for neurodegeneration in ALS. However, it cannot be considered as a validated surrogate endpoint for predicting efficacy yet for regulatory purpose.

ALSFRS-R at week 28 (study 101 Part C)

Change in ALSFRS-R total score over 28 weeks was assessed in the mITT population as the primary endpoint using joint rank test (JRT) in conjunction with multiple imputation (MI) for withdrawals other than death. In this subgroup, a non-statistically significant difference of 1.2 favouring tofersen was observed in ALSFRS-R change from baseline at Week 28 (95% CI, –3.2 to 5.5; p = 0.97 via JRT+MI). Therefore, the study has failed the pre-specified conditions.

Post hoc analyses performed in the overall ITT population, adjusting for baseline NfL as a covariate, show a 2.1-point treatment difference in favour of tofersen (~34% slowing of decline for tofersen relative to placebo) with greater statistical differentiation (95% CI: -0.33, 4.54; JRT+MI nominal p = 0.5015; ANCOVA+MI nominal p = 0.0904), but still non-significant.

SVC at week 28 (study 101 Part C)

The treatment difference favoured the tofersen group compared to the placebo group for both the mITT population (treatment difference of 7.9 in percent predicted SVC change from baseline at Week 28 [95% CI: -3.5, 19.3]; nominal p = 0.323 [JRT+MI]) and the non-mITT population (treatment differences of 4.6 [95% CI: –1.2, 10.5]). Additional analyses in the faster-progressing NfL subgroup (baseline plasma NfL ≥ median) and in the overall ITT population adjusting for baseline NfL as a covariate have shown largely similar treatment differences, numerically favouring tofersen. None of the analyses demonstrated statistically significant differences.

HHD Megascore at week 28 (study 101 Part C)

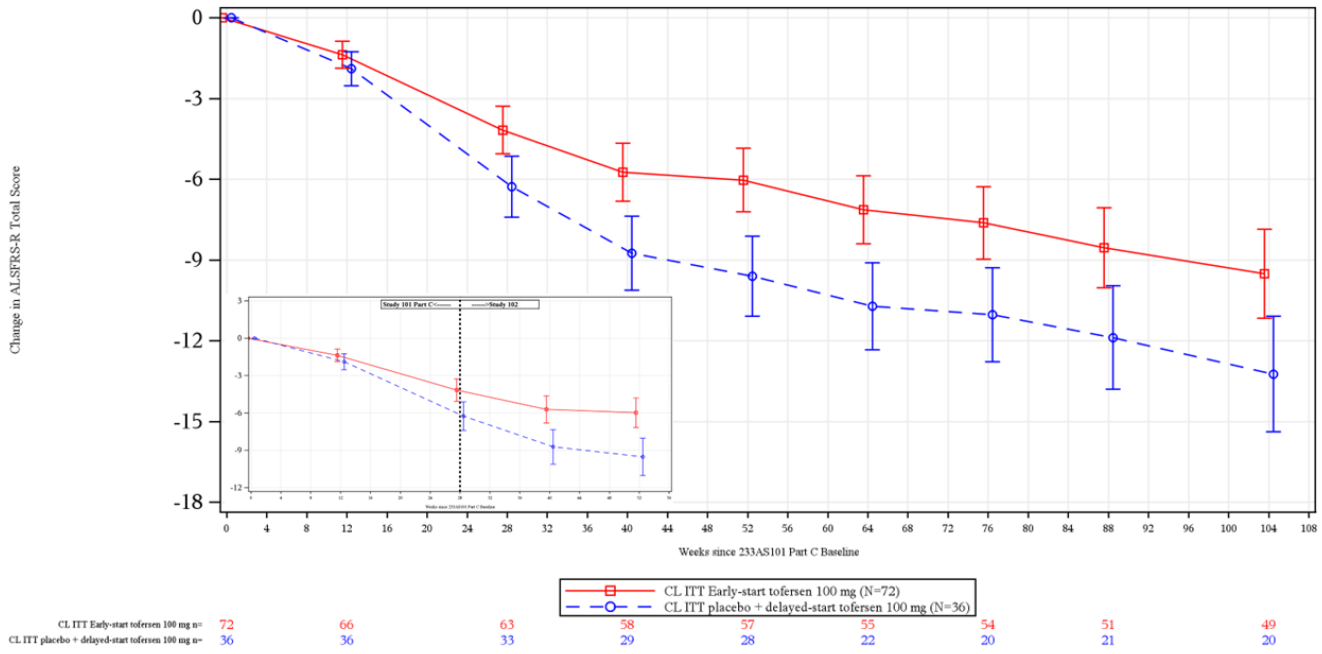
Modest trends suggesting slowing of decline in muscle strength were observed with tofersen administration in the mITT and non-mITT populations: differences of 0.02 (95% CI: -0.21, 0.26) and 0.09 (95% CI: -0.08, 0.26) favoring tofersen were observed, respectively. These trends were most apparent in lower limb muscles as compared with upper limb muscles. Additional analyses in the faster-progressing NfL subgroup (baseline plasma NfL ≥ median) and in the overall ITT population adjusting for baseline NfL as a covariate have shown largely similar (though slightly higher) treatment differences which numerically favoured tofersen. None of the analyses demonstrated statistically significant differences.

In view of the above 28-week data from the pivotal study 101 part C and the fact that neither the pre-specified primary efficacy analysis nor the additional analyses of the primary and key secondary functional endpoints have demonstrated statistically significant effects and can generally be judged as rather modest treatment effects, the COMP put particular emphasis on long-term trends comparing functional effects in the 'early-start group' with the one of the 'delayed-start group' over 104 weeks, see Figure 1 above.

ALSFRS-R at week 52 and 104 (pooled efficacy data: study 101 Part C + OLE Study 102)

A continued separation between the placebo/delayed-start participants and the early-start tofersen treatment group over the longer-term in the overall ITT population adjusted for baseline plasma NfL through Week 52 and 104 was observed (Figure 2). A post-doc analysis of change in ALSFRS-R total score over 52 weeks show a 3.5 point treatment difference in favour of tofersen with greater statistical differentiation (95% CI: -0.4, 6.7; ANCOVA+MI nominal p = 0.0272). This data suggests that the study might have reached its pre-specified primary endpoint with statistically significant difference, if the duration of the study with a placebo control would have been 52 instead of 28 weeks. A post-hoc analysis of change in ALSFRS-R total score over 104 weeks show a 3.7 point treatment difference in favour of tofersen (95% CI: -0.7, 8.2; ANCOVA+MI nominal p = 0.1004).

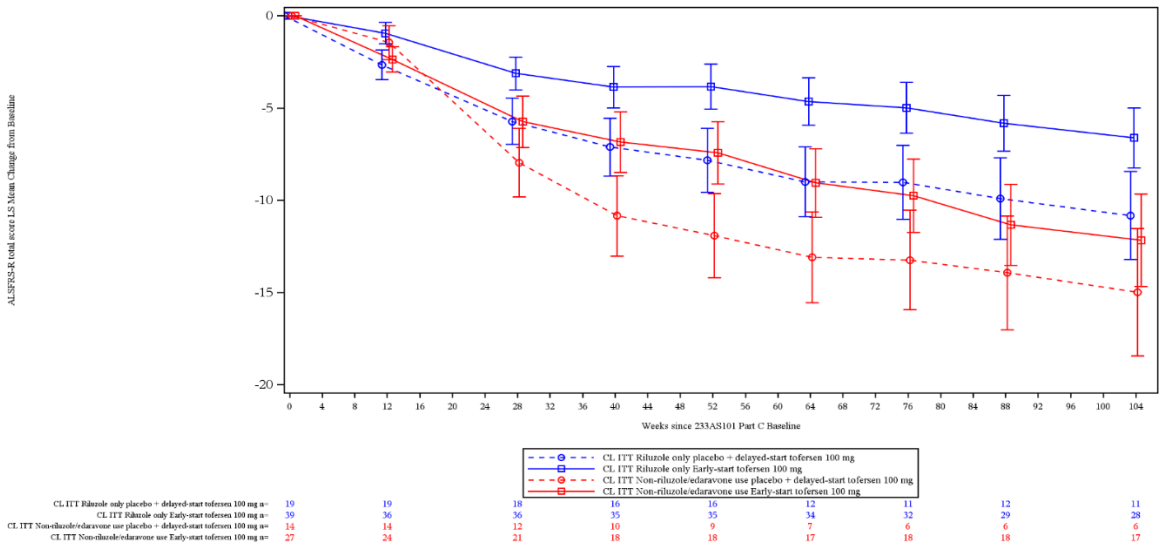
Figure 2. ALSFRS-R total score adjusted mean change from Study 101 Part C Baseline ±SE by Visit to Week 104 from ANCOVA+MI - ITT Population adjusted for Baseline plasma NfL (insert: to Week 52)



Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation. Source: biib067/ise/ise-bla4/f-cf-alsf-ancmi-cl12-itt.sas Data Cutoff: 28FEB2023 Run Date: 05JUN2023

Of note, this general trend of ALSFRS-R scores favouring tofersen treatment was consistently observed across different populations and disease progression subgroups (mITT vs. non-mITT and NfL-based), regardless of which covariates were adjusted for. This trend of ALSFRS-R scores favouring tofersen treatment was also observed in the population adjusted for riluzole use (Figure 3), suggesting an additional benefit when tofersen was used in combination with riluzole over riluzole alone.

Figure 3. ALSFRS-R total score LS mean change from baseline values ± SE by time point from ANCOVA analysis using MI for pooled group CL by baseline riluzole use - ITT population excluding participants who used edaravone



Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation. Source: biib067/ema/orphandd/f-cf-alsf-anc-clitt-ril-v2.sas Data Cutoff: 28FEB2023 Run Date: 08AUG2023

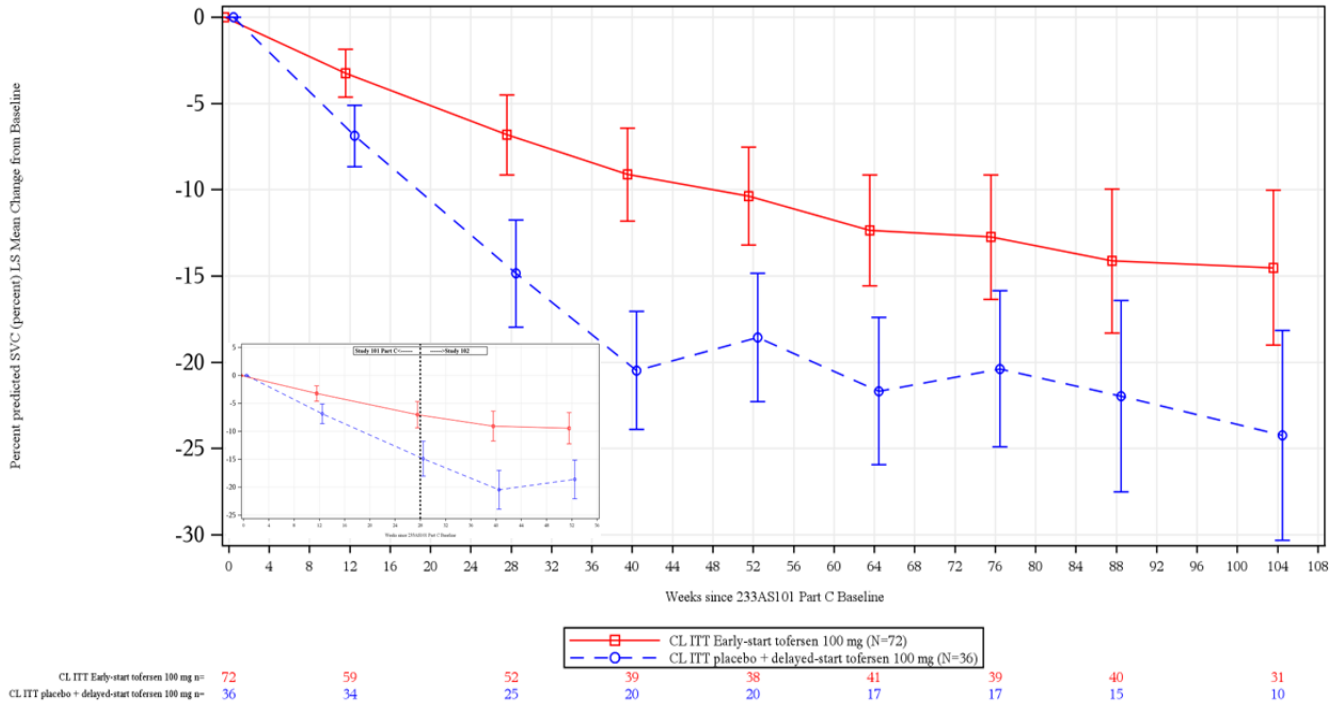
Although the decline in ALSFRS-R is not always linear, it is estimated that people living with ALS decline by an average of approximately 1 point per month. Participants in Studies 101 Part C and 102 lost 9.5 and 13.2 points (adjusted mean on ANCOVA+MI) over 24 months in the tofersen early-start and placebo/delayed-start groups, respectively, which is not consistent with the described natural course of the disease in the literature.

SVC at week 52 and 104 (pooled efficacy data: study 101 Part C + OLE Study 102)

A continued separation between the treatment groups over the longer-term was observed also for respiratory function (Figure 4). Notably in the placebo/delayed-start group, declines appeared to stabilize after Week 40, approximately 12 weeks after initiation of tofersen and the time point at which maximum biological activity would be expected. At Week 52 a 9.2 percent-predicted difference in SVC between early-start and placebo/delayed-start tofersen arms were seen (95% CI: 1.7, 16.6; nominal p=0.0159). At Week 104 a 9.7 percent-predicted difference in SVC between early-start and placebo/delayed-start tofersen arms were seen (95% CI: -0.8, 20.2; nominal p=0.0702).

Additional analyses showed that participants treated with tofersen reported improvement irrespective of whether they received concomitant riluzole.

Figure 4. Percent-predicted **SVC** adjusted mean change from Study 101 Part C Baseline ±SE by Visit to Week 104 from ANCOVA+MI - ITT Population adjusted for Baseline plasma NfL (insert: to Week 52)



Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square. Source: biib067/ise/ise-bla4/f-cf-svc-ancmi-cl12-itt.sas Data Cutoff: 28FEB2023 Run Date: 05JUN2023

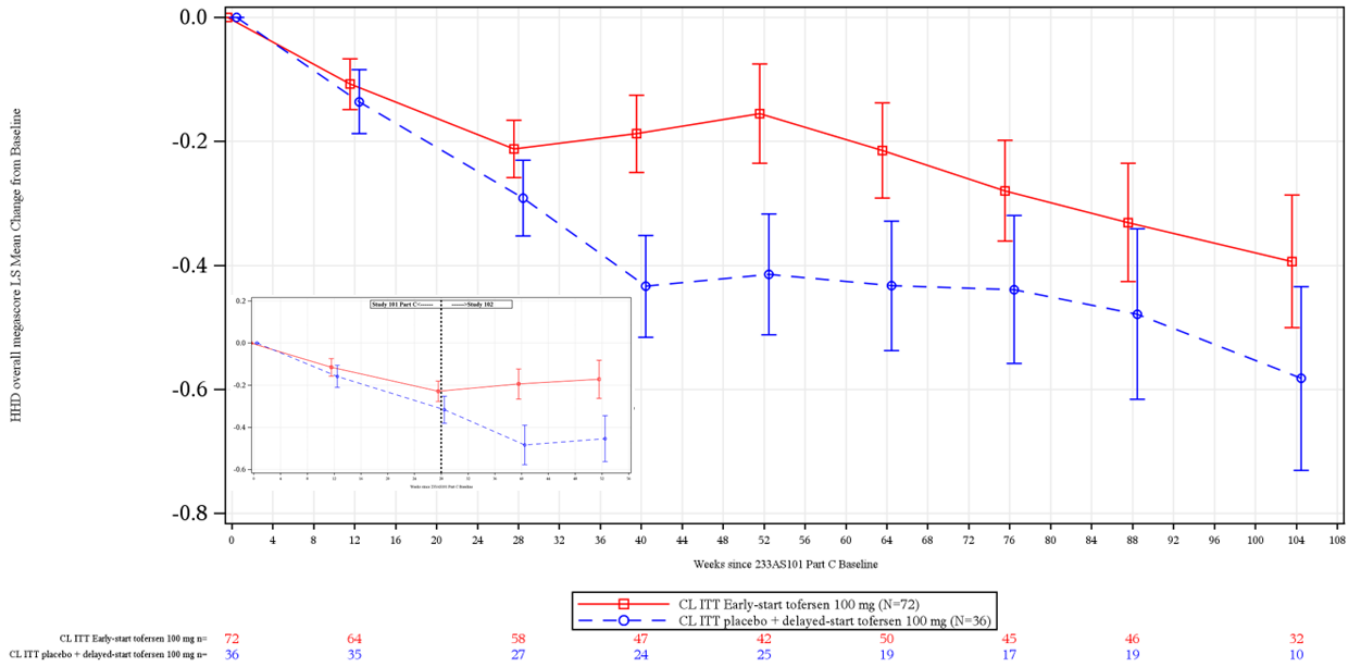
HHD Megascore at week 52 and 104 (pooled efficacy data: study 101 Part C + OLE Study 102)

The general trend in HHD megascore in favour of early-start tofersen was maintained throughout week 52 and 104 (Figure 5), and irrespective of riluzole use. At Week 52 differences of 0.28 (95% CI: 0.047,

0.517; p-value (ANCOVA+MI): 0.0186) and at week 104 differences of 0.2 (95% CI: -0.10, 0.47; p-value (ANCOVA+MI): 0.1946) favoring tofersen were observed, respectively. Participants reported improvement irrespective of whether they received concomitant riluzole or not.

Putting these results into context, ALS patients generally experience continuous and progressive loss in muscle strength; a liner decline in HHD megascore of ~1.4 over 52 weeks (0.04/week) has been reported in 'all comers' ALS populations from 2 recently conducted clinical trials [Shefner 2018; Cudkowicz 2013; Cudkowicz 2014]. The data presented therefore at week 52 is not consistent with the more rapid decline described for the natural history of the disease.

Figure 5. HHD megascore adjusted mean change from Study 101 Part C Baseline ±SE by Visit to Week 104 from ANCOVA+MI - ITT Population adjusted for Baseline plasma NfL (insert: to Week 52)



Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square. Source: biib067/ise/ise-bla4/f-cf-mega-ancmi-cl12-itt.sas Data Cutoff: 28FEB2023 Run Date: 05JUN2023

In conclusion, contrary to the pre-planned primary efficacy analysis at week 28, the post-hoc analyses of the pooled dataset for the ITT population with baseline plasma NfL as a covariate at week 52 showed nominally statistically significant differences between early treatment tofersen and placebo/delayed treatment tofersen for all functional endpoints including ALSFRS-R, SVC and HDD megascore. The analyses at week 104 show some attenuation as compared to week 52, but a clear and largely similar difference still exists. This observed stabilisation would be supportive of a true disease modifying effect of tofersen, indicating also a greater benefit with early treatment start.

Responder analyses

The sponsor also performed responder analyses without or with logistic regression (i.e. adjustment of baseline NfL). Both analyses indicate a slowing of decline and even an improvement in muscle and respiratory function and muscle strength for the early and placebo/delayed start tofersen treatment group with a clear difference between groups and are considered unexpected when comparing to the described course of the disease from available natural history data. It appears as if early initiation of

tofersen treatment may be more beneficial compared to a delayed start. Some response was also seen in the placebo/delayed start tofersen treatment group.

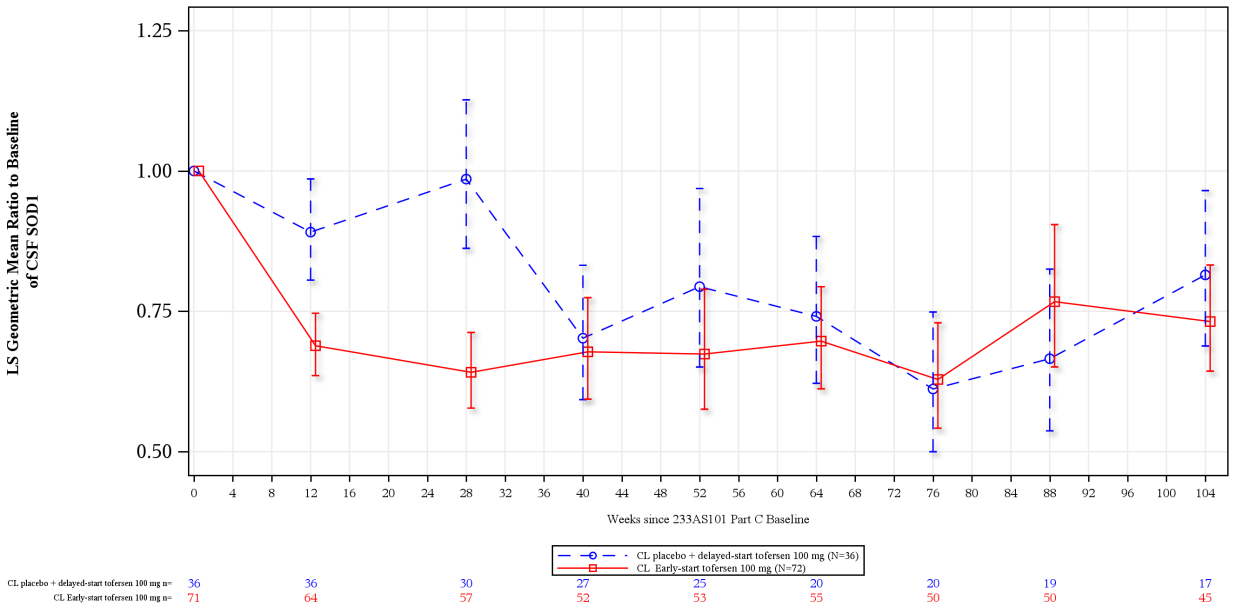
Biomarkers: SOD1 and NfL up to week 104

The COMP took note of the specific mechanism of action of tofersen which creates a strong mechanistic basis for use in the target patient population of ALS patients with SOD1 mutations. Throughout Study 101 Part C and Study 102, sustained significant reductions in the accumulation of toxic SOD1 levels were observed, as measured in patients CSF. These in turn were associated with disease-modifying effects, as measured by changes in plasma neurofilament (NfL) levels, a biomarker for neurodegeneration which is increasingly used in ALS.

It is observed that the reduction of SOD1 in the case of the early start tofersen treatment group achieves a noticeable decrease at week 12 and reaches the lowest point at week 28, after which it remains at decreased levels until week 104 (Figure 6). Levels of NfL reached their nadir by approximately 16 weeks after tofersen administration (Figure 7). The graphical pattern of the levels of NfL is quite similar to the graphical pattern of SOD1 with a time delay.

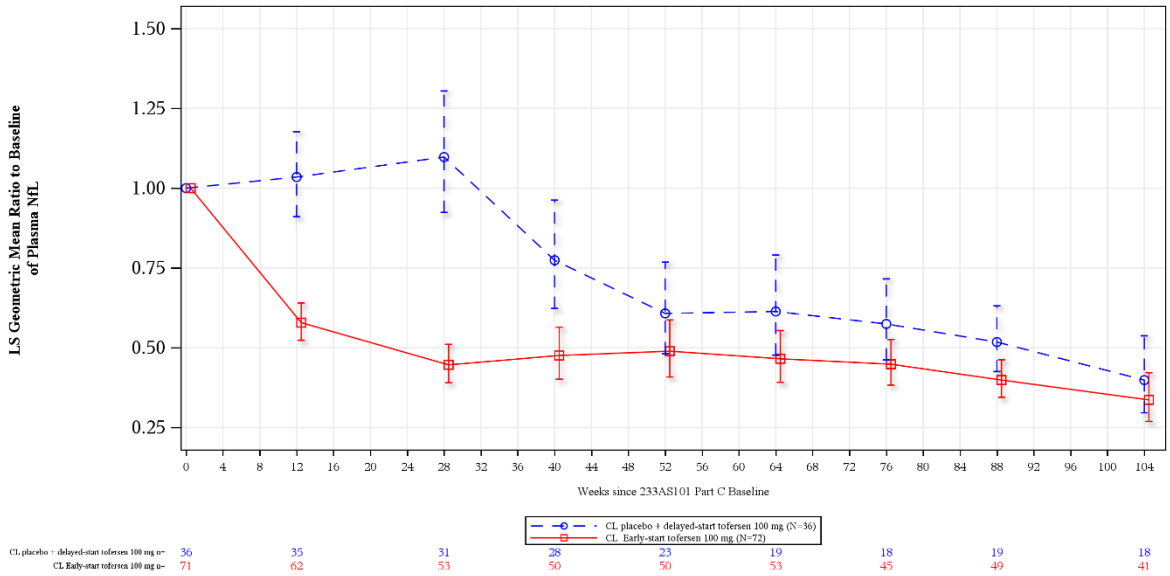
While NfL cannot be considered as a validated surrogate endpoint for predicting efficacy, the consistent reductions in CSF SOD1 and plasma Nf are supporting the biological plausibility with target engagement and a strong mechanistic rationale for the effect of tofersen treatment.

Figure 6. Pooled data Study 101 Part C and Study 102: Line plot of total CSF SOD1 protein LS geometric mean ratio to baseline values (95% CI) by time point (up to week 104) from ANCOVA analysis using MI - ITT population



Abbreviations: CSF = cerebrospinal fluid; SOD1 = superoxide dismutase 1; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/ise/ise-bla4/f-pkpd-sod-anc-clitt.sas Data Cutoff: 28FEB2023 Run Date: 12JUN2023

Figure 7. Pooled data Study 101 Part C and Study 102: Plasma NfL Adjusted Geometric Mean Ratio to Study 101 Part C Baseline (95% Confidence Interval [CI]) by Visit to Week 104 From ANCOVA Using Multiple Imputation (MI) – ITT Population



Abbreviations: CSF = cerebrospinal fluid; SOD1 = superoxide dismutase 1; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/ise/ise-bla4/f-pkpd-sod-anc-clitt.sas Data Cutoff: 28FEB2023 Run Date: 12JUN2023

The sponsor points out that the timely effects on the biomarkers in relation to those on the clinical outcome measures suggest that the reductions in SOD1 protein and consequently NfL result in a delayed effect on function as measured by ALSFRS-R and other clinical outcome measures. The sponsor states that this is "*highlighting the time needed for a slowing of neurodegeneration to translate to detectable slowing of clinical decline*". This is considered to be biologically plausible by the COMP.

Survival at week 104 (pooled efficacy data: study 101 Part C + OLE Study 102)

Even though survival data was not considered by the COMP in the significant benefit assessment, the committee noted that an extended duration of follow-up from baseline to 3.4 years showed that the majority of patients remain alive on-study. The range of follow-up from 2.2 to 3.9 years exceeds the 2.3 years median survival for SOD1-ALS characterized in the literature. Survival was numerically in favour for early start tofersen, relative to the delayed-start participants, which is considered unlikely to be attributed to enrolment of individuals with more slowly progressing disease.

Overall COMP conclusion

Tofersen-driven reductions in SOD1 protein in CSF over 104 weeks led to a sustained slowing of the neurodegenerative process, as evidenced by robust reductions in NfL over the same period.

Although a statistically significant difference was not observed on the primary analysis at Week 28 in Study 101 Part C, by Week 52, clear and meaningful differences favouring early-start tofersen (as compared with delayed- start tofersen) were observed across clinical outcome measures of clinical function (ALSFRS-R), respiratory strength (SVC), muscle strength (HHD megascore).

With longer follow-up to 104, there is some apparent convergence of effect between treatment arms, as the placebo/delayed-start group had the opportunity to cross-over to active tofersen at Week 28; however, the differences between arms remain clinically meaningful.

Further, the magnitudes of slowing in progression on each of these endpoints when compared with the natural history of ALS/SOD1-ALS, coupled with the nearly 1 in 5 participants experiencing improvement on each of these endpoints over 104 weeks of tofersen treatment, are so at odds with disease natural history, that they are considered to meet the significant benefit criterion for orphan maintenance of a clinically relevant advantage due to improved efficacy, more so, given that riluzole has no effect on clinical function or strength.

The COMP adopted a positive opinion.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 23 February 2024

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of amyotrophic lateral sclerosis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.7 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life-threatening due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure with shortened life expectancy;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the claim that Qalsody is of significant benefit to those affected by the orphan condition is established. The sponsor has provided clinical data in ALS patients with confirmed mutations in the *SOD1* gene that, in totality, indicate effects on functional outcomes including motor function, respiratory function and muscle strength, which cannot be expected from the currently authorized medicinal product. The Committee considered that this constitutes a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Qalsody, synthetic ribonucleic acid oligonucleotide directed against superoxide dismutase 1 messenger ribonucleic acid, tofersen for treatment of amyotrophic lateral sclerosis (EU/3/16/1732) is not removed from the Community Register of Orphan Medicinal Products.