Report QALSODY® - Tofersen

Product & Mechanism of action

Substance: Tofersen

Brand Name: Qalsody

Originator/licensee: Biogen Netherlands B.V.

Classification: NCE

ATC code: N07XX22

Orphan Status:
Eu: No
Us: Yes

Mechanism of action:
Tofersen is an antisense oligonucleotide that binds to the mRNA of the SOD1 gene, leading to its breakdown and a reduction in the amount of SOD1 protein produced [1].

Authorized indications Licensing status

Authorized Indication:
EMA: Tofersen is indicated for the treatment of adults with ALS associated with a mutation in the SOD1 gene [1].

FDA: Tofersen is an antisense oligonucleotide indicated for the treatment of ALS in adults who have a mutation in the SOD1 gene [2].

Route of administration: INTRATHECALLY

Licensing status
EU CHMP P.O. date: 22/02/2024
FDA M.A. date: 25/04/2023

EU Speed Approval Pathway: Yes
FDA Speed Approval Pathway: Yes

ABBREVIATIONS:
AE: Adverse Event
ALS: Amyotrophic Lateral Sclerosis
ALSFRS-R: ALS Functional Rating Scale-Revised
CHMP: Committee for Medicinal Products for Human Use
CNS: Central Nervous System
CSF: Cerebrospinal Fluid
M.A.: Marketing Authorization
NfL: Neurofilament Light chain
P.O.: Positive Opinion
Pts: Patients
SAE: Serious Adverse Event
SOD: Superoxie Dismutase
TEAE: Treatment Emergent Adverse Event

Essential therapeutic features

Summary of clinical EFFICACY:
VALOR (NCT02623699) in this phase 3, double-blind trial, adults (n=108) with SOD1 ALS were randomly assigned in a 2:1 ratio to receive eight doses of tofersen (100 mg through a lumbar puncture of a 15ml solution; n=72) or an equivalent volume of placebo (n=36).
This is part C of a three-part trial, the first two parts of which were dose-escalation trials conducted to assess the dose of tofersen to be used in part C.
The part C included a 4-week screening period, a 24-week treatment period, and a follow-up period of 4 to 8 weeks followed by an ongoing extension phase.
The primary end point was the change from baseline to week 28 in the total score on the ALSFRS–R (12 items across bulbar, fine motor, gross motor and breath functions; range 0 to 48, with higher scores indicating better function) among pts who met the trial-defined prognostic criteria for faster-progressing disease (who represent the primary analysis population; n=60 of 108 pts).
Pts with slower-progressing disease were not included in the primary end-point analysis but had the opportunity to be enrolled in the open-label extension to receive tofersen.
Participants who initiated tofersen in VALOR are referred to as the "early-start cohort," regardless of whether they were predicted to have faster-progressing or slower-progressing disease in the randomized part of the trial. Those who received placebo in VALOR and had the opportunity to cross over to tofersen in the open-label extension, approximately 28 weeks later, are referred to as the "delayed-start cohort."
Among the 60 pts belong to the faster-progression primary analysis subgroup, the change to week 28 in the ALSFRS-R total score was -6.98 with tofersen and -8.14 with placebo (difference, 1.2 points; 95% CI, -3.2 to 5.5; P = 0.97). The difference was not statistical significant [3].

VALOR (NCT02623699) Part C	Partecipants (n=108)			
	Faster-progression disease (n=60)		Slower-progression disease (n=48)	
	Early-start cohort	Delay-start cohort	Early-start cohort	Delay-start cohort
	Tofersen (n=39)	Placebo (n=21)	Tofersen (n=33)	Placebo (n=15)
ASLFRS-R baseline score	36.0	35.4	38.1	39.9
Change from baseline ASLFRS-R score to week 28 (primary end point)	-6,98	-8,14	-1.33	-2.73

Summary of clinical SAFETY:
Nearly all subjects had at least 1 TEAE; most events were mild to moderate in severity and did not cause withdrawal or discontinuation of the trial agent. Most AEs were consistent with ALS disease progression, conditions in the general population, or known side effects of lumbar puncture.
The most common AEs included procedural pain, headache, pain in the arms or legs, falls, and back pain. The incidence of procedural pain (57%) and headache (46%) were similar among participants who received tofersen and among those who received placebo, whereas pain in the arms or legs and back pain were more common in the tofersen group (incidence higher by ≥5%) [3].
Several participants treated with tofersen had SAEs involving the CNS, no similar events were reported in the placebo group [4].

SAE (VALOR treatment period)	**Tofersen 100 mg (N=72) n (%)**
Subjects with serious neurologic events	4 (5.6)
Myelitis / Transverse myelitis	2 (2.8)
Meningitis chemical	1 (1.4)
Lumbar radiculopathy	1 (1.4)
Nervous system disorder	0

Ongoing studies:
- ***For the same indication:*** *Yes*
- ***For other indication:*** *No*

Discontinued studies (for the same indication): No

References:
[1] https://www.ema.europa.eu/en/medicines/human/variation/aspaveli
[2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215887Orig1s000Correctedlbl.pdf
[3] https://www.nejm.org/doi/10.1056/NEJMoa2204705?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
[4] https://biogen.gcs-web.com/static-files/b2154d4e-f69f-49d4-9a61-e834387293ea
[5] https://www.osservatoriomalattierare.it/malattie-rare/sla
[6] https://www.io.nihr.ac.uk/techbriefings/tofersen-for-the-treatment-of-amyotrophic-lateral-sclerosis-caused-by-mutations-in-the-sod1-gene/

NHS impact

Cost of therapy:
The price is not available yet.

Epidemiology:
A systematic review of global epidemiology of ALS reports a European median incidence rate of 1-3 cases per 100,000 inhabitants per year, corresponding to an estimated 15,355 cases.
In Italy there are at least 3,500 pts and 1,000 new cases every year [5-6].

POSSIBLE PLACE IN THERAPY:
There is no cure for ALS. Management consists of symptomatic and palliative care.
Riluzole is currently the only drug licensed for treating ALS with the indication of extend life or the time to mechanical ventilation for individuals with ALS.
Tofersen will offer a treatment option for pts with ALS caused by confirmed mutations in the SOD1 gene, who currently have no effective therapies available.

OTHER INDICATIONS IN DEVELOPMENT: -

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT: -

OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION: RAG-17 (study of safety and tolerability in pts with SOD1 ASL); Gene therapy AMT-162 (safety, tolerability and efficacy study).

*Service reorganization:
*Possible off label use:

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