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ASO drug Qalsody (tofersen) targets amyotrophic lateral sclerosis

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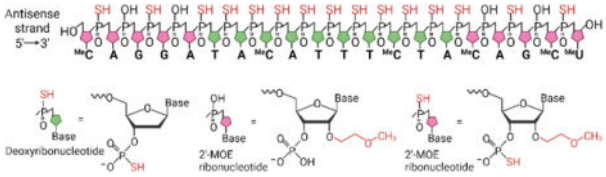
Graphical Abstract



STRUCTURE: Tofersen, an antisense oligonucleotide (ASO) drug, is a 20-base residue with an RNA-DNA-RNA (5-10-5) gapmer mixed backbone oligonucleotide. Within the molecule, there are nineteen inter-nucleotide linkages, with fifteen of them being 3'-O to 5'-O phosphorothioate diesters and the remaining four being 3'-O to 5'-O phosphate diesters. In terms of sugar residues, ten out of the twenty are 2-deoxy-D-ribose, while the others consist of 2'-O-(2-methoxyethyl)-D-ribose (2'-MOE). The arrangement of residues involves five MOE nucleosides located at both the 5' and 3'-ends, surrounding a central gap containing ten 2'-MOE. ^{Me} indicates that the cytosine and uridine bases are methylated at the 5-position. Tofersen's molecular formula is $C_{230}H_{317}N_{72}O_{123}P_{19}S_{15}$, and it possesses a molecular weight of 7127.86 atomic mass units.

Graphical Abstract

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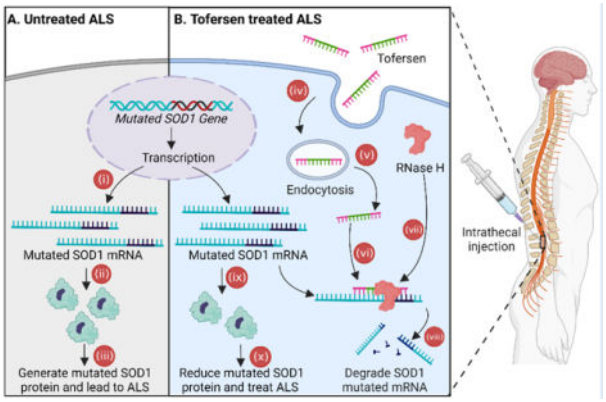
Declaration of interests
The authors declare no conflict of interest.



MECHANISM OF ACTION: (A) Approximately 2% of cases of amyotrophic lateral sclerosis (ALS) in adults is caused by a genetic mutation in the superoxide dismutase 1 (*SOD1*) gene. This mutation results in (i) the production of mutated SOD1 mRNA, which is then (ii) translated into dysfunctional SOD1 protein, (iii) contributing to the development of ALS. (B) Tofersen is indicated for the treatment of ALS in adults who have the mutation in the *SOD1* gene. Tofersen molecules enter motor neurons and astrocytes through (iv) endocytosis, with some molecules (v) escaping the endosomal pathway. Once inside the cytoplasm, (vi) tofersen binds to the mutated SOD1 mRNA, forming a DNA:RNA heteroduplex structure. (vii) The enzyme RNase H recognizes this hybrid chain and (viii) subsequently cleaves the mRNA, (ix) leading to a reduction in the production of mutated SOD1 protein. By inhibiting the synthesis of dysfunctional SOD1 protein, (x) tofersen offers a therapeutic approach for the treatment of ALS.

Acknowledgments

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Literature

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NAME:

The drug name is tofersen and the brand name is Qalsody.

DRUG CLASS:

Tofersen belongs to a large molecule class of drugs known as antisense oligonucleotides (ASO) therapeutics. It is an orphan drug with an accelerated approval.

CLINICAL USE:

Tofersen is an intrathecally administered therapeutic indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adult patients with a confirmed mutation in the superoxide dismutase 1 (*SOD1*) gene. The recommended dose for tofersen is 100 mg (15 mL). The treatment protocol involves an initial phase consisting of three loading doses administered at 14-day intervals. Following this phase, a maintenance dose should be administered once every 28 days thereafter.

DEVELOPED BY:

Tofersen was developed by Ionis Pharmaceuticals. Biogen licensed tofersen from Ionis Pharmaceuticals under a collaborative development and license agreement.

ADVERSE EFFECTS:

The most common adverse reactions are pain, fatigue, arthralgia, cerebrospinal fluid white blood cell counts increase, and myalgia. It is important to highlight other certain clinically adverse reactions associated with the treatment, including myelitis and/or radiculitis, papilledema, elevated intracranial pressure, and aseptic meningitis. These adverse reactions require attention due to their potential impact on patient health and well-being.

TIMELINE:

2015–2021: Phase 1/2/3 trial (NCT03764488 VALOR, NCT02623699 VALOR)

2017–present: Phase 3 trials (still recruiting) (NCT03070119 OLE, NCT04856982 ATLAS)

4/25/2023: FDA approval for Qalsody (tofersen), application number: 215887.