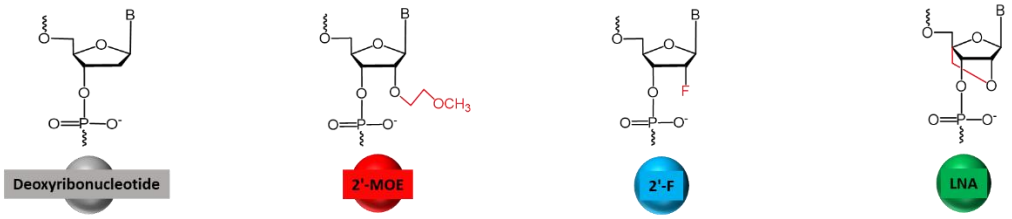
Supplementary information

Table S1. Results of clinical investigations of FDA-approved ASOs.

No.	ASO drug	Result of clinical studies		Ref.
		Efficacy	Side effects	
1	Fomivirsen (Vitravene®)	Treatment of fomivirsen significantly delayed the progression of CMV retinitis in patients with AIDS. The treatment also significantly delayed CMV retinitis progression in patients with advanced, refractory, sight-threatening disease.	Mild-to-moderate transient increase of intraocular pressure and intraocular inflammation.	206
2	Mipomersen (Kynamro®)	Mipomersen is a pharmacologic option for lowering low-density lipoprotein-cholesterol (LDL-C) in patients with severe hypercholesterolemia, as treatment of mipomersen significantly reduced LDL-C, apolipoprotein B and lipoprotein(a), with no change in high-density lipoprotein cholesterol (HDL-C) in patients.	Mild-to-moderate injection site reactions and flu-like symptoms (frequently reported); increased alanine transaminase, aspartate transaminase, and hepatic steatosis (occurred in ~10-20%).	207
3	Eteplirsen (Exondys 51®)	Treatment of eteplirsen was observed to delay the progression of DMD in terms of ambulatory ability as measured by the 6-minute walking test (6MWT). Eteplirsen is beneficial for patients with DMD with deletion mutation (deletions ending at exon-50 and starting at exon-52, covering ~20.5% of patients with deletion mutations, or 14% of all patients).	Vomiting, headaches, balance disorder, and proteinuria (occurred in about half of patients).	14, 208, 209
4	Nusinersen (Spinraza®)	Nusinersen treatment significantly lowered the incidence of the use of permanent assisted ventilation, and clinically enhanced at least two motor skills of patients with SMA. The treatment also lowered the percentage of mortality of infants with SMA.	Procedural headache, procedural pain, procedural nausea, puncture syndrome, fluid leakage, vomiting, and cerebrospinal.	210
5	Inotersen (Tegsedi®)	Inotersen treatment improved the course of neuropathy and quality of life in patients with hereditary TTR amyloidosis.	Glomerulonephritis and thrombocytopenia.	211
6	Golodirsen (Vyondys 53®)	Treatment of golodirsen increased the production of functional dystrophin in skeletal muscle. Golodirsen is beneficial for DMD patients with confirmed mutation of the *DMD* gene amenable to exon-53 skipping, which represents ~8% of all DMD patients.	Headache, pyrexia, abdominal pain, nasopharyngitis, vomiting, nausea, cough, and fall.	23
7	Viltolarsen (Viltepso®)	Treatment of viltolarsen induced dystrophin expression in DMD patients with confirmed mutation of the *DMD* gene amenable to exon-53 skipping, which represents ~8% of all DMD patients. The treatment also significantly improved the results of tests including the time to stand from supine position, run/walk 10 m, and 6MWT.	Cough, vomiting, nasopharyngitis, upper respiratory tract infection, and diarrhea.	24
8	Casimersen (Amondys 45®)	Treatment of casimersen induced dystrophin expression in DMD patients with confirmed mutation of the *DMD* gene amenable to exon-45 skipping, which represents ~7% of all DMD patients.	Upper respiratory tract infection, cough, pyrexia, headache, arthralgia and oropharyngeal pain	25



Examples of ASO design	Mechanism of action	Features
Unmodified DNA	Induction of RNase H mediated mRNA degradation	Poor nuclease stability and binding affinity
5-10-5 MOE-DNA-MOE gapmer	Induction of RNase H mediated mRNA degradation (the central DNA sequence recruits RNase H)	Improved nuclease stability and binding affinity compared to unmodified DNA
Uniformly modified 2'-MOE ASO 2-16-2 LNA-MOE-LNA gapmer 2'-F/LNA mixmer	Steric blockade leading to splice modulation or translational repression (these ASOs do not possess unmodified DNA sequence which is key to the RNase H recruitment, therefore, they are unable to induce RNase H mediated mRNA degradation)	Further improved nuclease stability and binding affinity compared to the unmodified DNA ASO and gapmer that contains unmodified central DNA sequence

Figure S1. The relationship between ASO design and the mechanism of action of ASOs.

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