Patisiran & Vutrisiran: Chemical and Molecular Differences

The following information is provided in response to your unsolicited inquiry. It is intended to provide you with a review of the available scientific literature and to assist you in forming your own conclusions in order to make healthcare decisions. This document is not for further dissemination or publication without authorization.

The full Prescribing Information for ONPATTRO® (patisiran) is provided here, and the full Prescribing Information for AMVUTTRA® (vutrisiran) is provided here. Alnylam Pharmaceuticals does not recommend the use of its products in any manner that is inconsistent with the approved Prescribing Information. This resource may contain information that is not in the approved Prescribing Information.

If you are seeking additional scientific information related to Alnylam medicines, you may visit the Alnylam US Medical Affairs website at RNAiScience.com.

SUMMARY

- Patisiran is an intravenously administered, TTR-directed siRNA formulated as a lipid complex for delivery to hepatocytes.[1]
- Vutrisiran is a subcutaneously administered, TTR-directed siRNA that is conjugated to GalNAc and utilizes ESC for improved molecular stability and minimized metabolic lability.[2,3]

INDEX

CHEMICAL DESCRIPTION

Patisiran

Patisiran is an intravenously administered double-stranded siRNA formulated as a lipid complex for delivery to hepatocytes. Patisiran specifically binds to a genetically conserved sequence in the 3'UTR of mutant and wild-type TTR mRNA.[1]

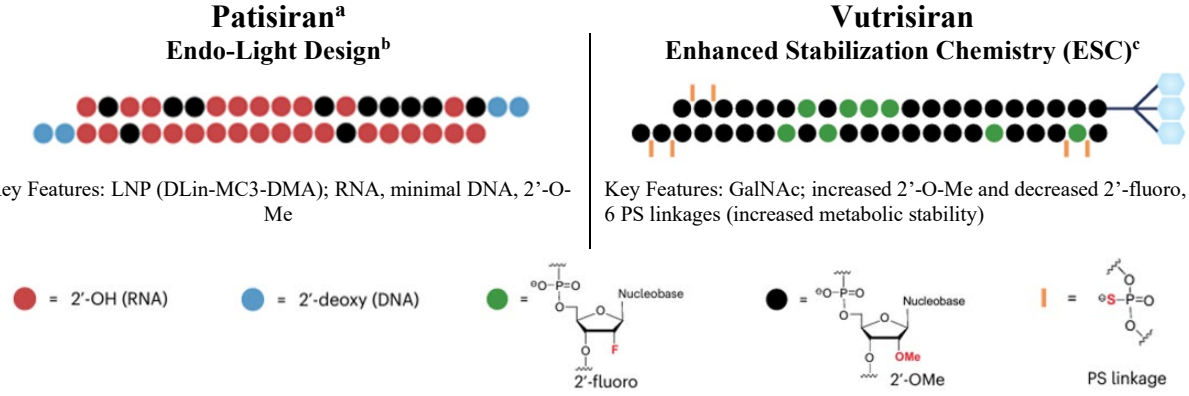
The molecular formula of patisiran sodium is C_{412} H_{480} N_{148} Na_{40} O_{290} P_{40} and the molecular weight is 14,304 Da.[1]

Vutrisiran

Vutrisiran is a subcutaneously administered double-stranded siRNA that targets mutant and wild-type TTR mRNA and is covalently linked to a ligand containing 3 GalNAc residues to enable delivery of the siRNA to hepatocytes.[2] Vutrisiran utilizes second-generation ESC, which includes a combination of additional PS linkages, as well as 2′-O-methyl nucleotide and 2′-fluoro nucleotide modifications, which has improved molecular stability and minimized metabolic lability.[3,4]

The molecular formula of vutrisiran sodium is C_{530} H_{672} F_9 N_{171} Na_{43} O_{323} P_{43} S_6 with a molecular weight of 17,290 Da. The molecular formula of the free acid is C_{530} H_{715} F_9 N_{171} O_{323} P_{43} S_6 with a molecular weight of 16,345 Da.[2]

Figure 1. Differences between the Chemistries of Patisiran and Vutrisiran.[5]



Abbreviations: 2'-OH = 2'-O-hydroxyl; 2'-OMe = 2'-O-methyl; DNA = deoxyribonucleic acid; ESC = enhanced stabilization chemistry; GalNAc = N-acetylgalactosamine; LNP = lipid nanoparticle; MC3 = (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate (DLin-MC3-DMA); PS = phosphorothioate; RNA = ribonucleic acid; siRNA = small interfering RNA; SS = sense strand.
[a]Patisiran is based on partially modified siRNAs (endo-light design) formulated in MC3-containing second-generation LNPs. MC3 is an ionizable lipid that improved the potency of siRNAs delivered by LNPs by approximately 100-fold over that of previous LNP formulations.
[b]Conventional, partially modified symmetrical design that features 2-nucleotide DNA overhangs and a sequence-specific modification pattern (endo-light), with 2′-OMe modifications applied to all pyrimidines in the SS and to pyrimidines that are 5′ adjacent to the ribo A nucleoside.
[c]Fully modified 21- to 23-nucleotide siRNAs with 6 PS linkages and a single 2-nucleotide overhang.
From Jadhav et al[5]

ABBREVIATIONS

2'-OH = 2'-O-hydroxyl; 2'-OMe = 2'-O-methyl; 3'UTR = 3' untranslated region; DNA = deoxyribonucleic acid; ESC = enhanced stabilization chemistry; GalNAc = N-acetylgalactosamine; LNP = lipid nanoparticle; MC3 = (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino)butanoate (DLin-MC3-DMA); mRNA = messenger RNA; PS = phosphorothioate; RNA = ribonucleic acid; siRNA = small interfering RNA; SS = sense strand; TTR = transthyretin.

Updated 20 September 2024

REFERENCES

1. ONPATTRO (patisiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.
2. AMVUTTRA (vutrisiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.
3. Habtemariam BA, Karsten V, Attarwala H, et al. Single-dose pharmacokinetics and pharmacodynamics of transthyretin targeting N-acetylgalactosamine–small interfering ribonucleic acid conjugate, vutrisiran, in healthy subjects. *Clin Pharmacol Ther*. 2021;109(2):372-382. doi:10.1002/cpt.1974
4. Janas MM, Zlatev I, Liu J, et al. Safety evaluation of 2'-deoxy-2'-fluoro nucleotides in GalNAc-siRNA conjugates. *Nucleic Acids Res*. 2019;47(7):3306-3320. doi:10.1093/nar/gkz140
5. Jadhav V, Vaishnaw A, Fitzgerald K, Maier MA. RNA interference in the era of nucleic acid therapeutics. *Nat Biotechnol*. 2024;42(3):394-405. doi:10.1038/s41587-023-02105-y