
ALN-PCSsc

An RNAi therapeutic developed by Alnylam that targets the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene for the treatment of severe hypercholesterolemia.

Antisense technology

A drug discovery platform, which is designed to target and bind to RNA molecules, including messenger RNAs (mRNAs), and inhibit the production of disease-causing proteins.

Enzyme

A substance produced in an organism that acts as a catalyst, or chemical accelerator, to facilitate a specific biochemical reaction.

GalNAc-siRNA conjugates (galactose/N-acetylgalactosamine - short interfering ribonucleic acid conjugates)

A clinically validated, proprietary Alnylam delivery platform designed to achieve targeted delivery of RNA therapeutics to hepatocytes. This delivery platform enables specific, potent and durable knockdown of hepatocyte-expressed disease genes with subcutaneous dosing and a wide therapeutic index.

Gene regulation

A process in which a cell determines which genes are expressed when, for example, a skin cell turns on the genes that make it a skin cell, while a bone cell would leave these genes turned off. One of the most common ways gene regulation can be accomplished is by regulating the rate at which RNA transcription occurs.

Hemoglobin

A protein in red blood cells that carries oxygen throughout the body.

Hepatocyte

A chief functional cell of the liver, which performs a number of metabolic, endocrine and secretory functions including: protein storage, protein synthesis, transformation of carbohydrates, and the synthesis of cholesterol, bile salts and phospholipids. Roughly 80% of the mass of the liver is contributed by hepatocytes.

HDL cholesterol (high-density lipoprotein or HDL-c)

One of the five major groups of lipoproteins, HDL transfers fats away from cells, artery walls and tissues through the bloodstream. HDL is known as “good” cholesterol

because it deposits cholesterol in the liver, where it is excreted by the body. High HDL is thought to protect against coronary artery disease.

Hypercholesterolemia

A condition characterized by very high levels of cholesterol in the blood. The body needs cholesterol to build cell membranes, make certain hormones, and produce compounds that aid in fat digestion. Too much cholesterol however, increases a person's risk of developing heart disease.

Injection site reactions (ISRs)

An injection site reaction is inflammation in or damage to the tissue surrounding where a drug was injected. There are two types of injection site reactions. One is a local allergic reaction (or flare reaction), and is caused by drugs that are irritants. The other is a more severe reaction caused by extravasation, which is leakage of a small amount of drug from the blood vessel where it was injected. Symptoms for both reactions typically include redness, tenderness, warmth, and itching, but the consequences of extravasation are more severe and may include pain, blistering, and severe skin damage.

Investigational new drug (IND)

An application containing laboratory (pre-clinical) study results of a drug candidate, which is submitted to the FDA for review. If the application is cleared, the drug candidate usually enters a Phase I clinical trial.

Lipoprotein

A molecule made of proteins and fat, which carry all fat molecules (lipids) and similar substances through the blood.

LDL cholesterol (low lipid density lipoprotein or LDL-c)

Otherwise known as "bad" cholesterol, LDL is the cholesterol that is found in low-density lipoproteins (LDL). This type of cholesterol specifically collects in the walls of blood vessels, causing the blockages of atherosclerosis. Higher LDL levels can increase the risk of having a heart attack.

LDL receptor (low lipid density lipoprotein)

A protein found on the surface of cells. These receptors bind to particles called low-density lipoproteins (LDLs), which are the primary carriers of cholesterol in the blood. LDL receptors are particularly abundant in the liver, the organ responsible for removing most excess cholesterol from the body.

The number of LDL receptors on the surface of liver cells determines how quickly cholesterol (in the form of LDL) is removed from the bloodstream. Studies suggest that the PCSK9 protein helps control blood cholesterol levels by breaking down LDL receptors before they reach the cell surface.

mRNA (messenger ribonucleic acid)

A large family of RNA molecules that convey genetic information from DNA to the ribosome, where they specify the amino acid sequence of the protein products of gene expression.

Multi Dose (MD)

Utilizing or containing more than one dose.

Monoclonal antibody (mAb or moAb)

These laboratory generated molecules are carefully engineered to attach to specific defects in cells. Monoclonal antibodies mimic the antibodies the body naturally produces as part of the immune system's response to germs, vaccines and other invaders.

The Orion™ Development Program

The project name for the development program for ALN-PCSsc. Initial Phase 2 studies are planned to begin by the end of 2015, with a Phase 3 start expected in 2017. The Program will include a comparative study with anti-PCSK9 monoclonal antibodies.

PCSK9 gene (proprotein convertase subtilism/kexin type 9)

The PCSK9 gene provides instructions for making a protein that helps regulate the amount of cholesterol in the bloodstream. A mutation in this gene results in a slower metabolism of low-density lipoprotein cholesterol (LDL-c or "bad" cholesterol) in humans, thus resulting in the development of hypercholesterolemia and other related diseases.

PCSK9 protein (proprotein convertase subtilism/kexin type 9)

The PCSK9 protein appears to control the number of low-density lipoprotein (LDL) receptors. Studies suggest that the PCSK9 protein helps control blood cholesterol levels by breaking down LDL receptors before they reach the cell surface.

Pharmacokinetics

The study of the movement of drugs in the body including: the processes of absorption, distribution, localization in tissues, biotransformation, and excretion over time.

Pre-clinical trial

The study of a drug to assess the toxicity and examine its potential effects on the human body. Tests are conducted in test tubes or in animals before human clinical trials (Phase I) can be carried out.

Phase I clinical trial

The first set of studies to involve humans, and designed to evaluate the safety of a new drug.

Phase II clinical trial

A clinical study conducted after desired Phase I study results are achieved, to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition that is being studied. Phase II studies are also used to determine short-term side effects and risks.

Phase III clinical trial

Studies conducted after the completion of a Phase II clinical trial to compare the safety and effectiveness of a new drug against the current standard treatment.

RNA (Ribonucleic acid)

A single stranded molecule, which plays a major role in protein synthesis. RNA is involved in the transcription, decoding, and translation of the genetic code to produce proteins.

RNAa (Ribonucleic acid activation)

A small RNA-guided gene regulation mechanism, achieved by targeting carefully selected gene promoter regions using short double-stranded RNAs (dsRNAs).

RNAi (Ribonucleic acid interference)

A biological process in which RNA molecules inhibit gene expression, typically by causing the destruction of specific messenger RNA (mRNA) molecules.

Single Ascending Dose (SAD)

An ascending single dose study is typically conducted in 'First Time in Human' studies to identify the maximum tolerated dose and/or dose limiting toxicity. Unacceptable toxicity levels are determined based on pre-calculated pharmacokinetic safety levels.

siRNA (short interfering ribonucleic acid)

A small piece of double-stranded RNA (dsRNA) that can be used to "interfere" with the translation of proteins by binding to and promoting the degradation of messenger RNA (mRNA) at specific sequences. In doing so, siRNA prevents the production of specific proteins based on the nucleotide sequences of their corresponding mRNA.