Ascendis Pharma: transient drug conjugates

Ascendis Pharma's proprietary technology platform, TransCon, is a novel prodrug technology for the production of new patentable versions of drugs already on the market, which has been developed for improving the dosage form and effect in patients. A Phase II clinical study of Ascendis Pharma's most advanced drug candidate, a PEGylated growth hormone that only needs to be administered once-weekly to growth hormone-deficient adults, has recently produced promising results.

Dr. Dirk Vetter, CEO

Ascendis Pharma A/S is an emerging pharmaceutical company that specializes in new drug delivery versions of marketed drugs in the fields of endocrinology, central nervous system and infectious diseases. The parent company is headquartered in Copenhagen, Denmark. Ascendis Pharma maintains a research site (Ascendis Pharma GmbH) with 25 employees in the Heidelberg Technology Park under the management of Dr. Dirk Vetter. The company opened an office in Palo Alto, California (USA) in 2010, from where Jan Møller Mikkelsen, President and CEO of Ascendis Pharma, coordinates the company's business and strategic development. "We chose to set up an office in the Silicon Valley in order to improve our situation vis-à-vis American venture capital investors," said Vetter in an interview with BioRN in Heidelberg.

Ascendis was established in December 2007 with the acquisition of Complex Biosystems GmbH, founded by Dirk Vetter and Harald Rau in 2002. Ascendis Pharma's technology platform TransCon, initially developed by Complex Biosystems, enables the transient conjugation of drugs with different carriers, thereby improving the dosage form and effect of drugs already on the market. Rau is now the Chief Scientific Officer and, along with Dirk Vetter, is a member of the parent company's management team.

The TransCon linker technology

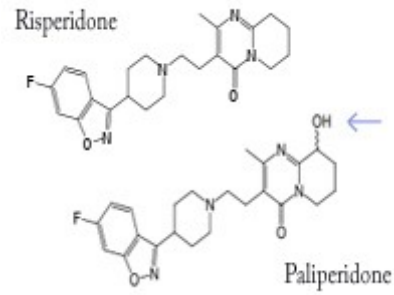
TransCon is a prodrug technology platform which enables the transient conjugation of small molecules, proteins and peptides to various carriers using the company's proprietary linker structures. Prodrugs are drugs administered in an inactive form, which are subsequently metabolized in vivo (i.e. in the patient) into an active metabolite. In contrast to other methods, which require a prodrug to be enzymatically cleaved into active metabolites in the body, the chemical properties of Ascendis Pharma's linkers are based on self-cleaving linkers that autohydrolyze in a non-enzymatic reaction. The unmodified drug component of the TransCon conjugate can then be released independently of the enzyme activity and tissue conditions. The autohydrolysis of the linker is determined solely by pH and temperature; the cleavage rates can thus be engineered to give an optimal pharmacokinetic profile for a given drug substance: the unmodified drug is released at a predictable rate and in a controlled manner in the body, thereby achieving a defined long-term effect.

Schematic of a conventionally PEGylated drug. The thread wound around the central molecule is polyethylene glycol.

The TransCon technology can be used for different drugs, including peptides, proteins and small molecules. Ascendis Pharma uses polyethylene glycol (PEG) as carrier molecule. The company uses either linear, branched or multi-arm PEG (TransCon PEG) or TransCon Hydrogel, which is a self-eliminating hydrogel. The TransCon technology can also be used to couple a number of drugs to an albumin carrier.

Other conjugation technologies, including the conventional PEGylation technology, are unable to release the conjugated drug in the same time-controlled manner as the TransCon technology. This is because the drug cannot be released because the polymer shuts it in like a cage, and is also less active. High-molecular PEGylated drugs cannot enter the tissue from the blood circulation into which it is injected. Higher concentrations need to be injected into the blood plasma in order to achieve the same effect as the TransCon technology. However, higher quantities of drugs are associated with undesired or dangerous side effects. The TransCon technology avoids this.

Ascendis Pharma's proprietary pipeline and outlicencing



Structural formula of the neuroleptic drug Risperidone and its major metabolite, Paliperidone.
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Ascendis Pharma's objective is to use its technology for the production of patentable, transiently conjugated prodrugs of marketed high-quality drugs, which are associated with a relatively minor clinical risk and can be brought to commercial maturity within a relatively short period of time. The company's drug pipeline is aimed at a global market with an annual volume of more than 13 billion US dollars. The company's proprietary pipeline currently consists of conjugated versions of drug hormones, the neuroleptic drug Paliperodone for the treatment of schizophrenic and bipolar patients, the dopamine antagonist Pramipexole for the treatment of early stages of Parkinson's disease and restless leg syndrome patients, as well as interferon alpha for the treatment of hepatitis C and factor IX for the treatment of haemophilia.

Three-dimensional model of human growth hormone
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The company's diabetes product pipeline – TransCon Hydrogel Insulin, TransCon Hydrogel GLP-1 (glucagon-like peptide 1) and a combination of the two – was sold to Sanofi-Aventis in December 2010. Pierre Chancel, Senior Vice President and Head of Sanofi-Aventis' Global Diabetes Division commented on the partnership agreement: "With this innovative TransCon linker technology, which has already shown promising results in preclinical studies on the delivery of insulin, we hope to offer biologics that present an extended and controlled release of parent drugs, including insulin. Under the terms of the agreement, Sanofi-Aventis was given a worldwide licence to develop, manufacture and commercialize products combining the technology with active molecules in diabetes and related

disorders. Ascendis received an upfront payment and is eligible for development, regulatory and specified commercial milestone payments.

TransCon PEG Growth Hormone (ACP-001)

ACP-001 (TransCon PEG Growth Hormone) is the most advanced drug candidate generated with the company's TransCon technology. The drug is designed to be used for the treatment of growth hormone deficiency in adult patients. In September 2011, the company successfully completed a Phase II clinical study. In contrast to an already approved growth hormone formulation, Ascendis Pharma's TransCon PEG Growth Hormone, administered over a period of four weeks once-weekly with a very fine needle, achieved the same effect as the equivalent dose of daily injections of daily growth hormone. The Phase II clinical study met the primary efficacy endpoint, which relates to the change in IGF-1 (insulin-like growth factor 1, a growth factor secreted into the blood by the liver upon the stimulation of growth hormone) levels. The change in IGF-I levels was proportional to the dosage and it was possible to maintain a physiological IGF-I level throughout the entire study period. No treatment-emergent anti-hGH antibody formation was observed during the trial.

ACP-001 administered once-weekly was as effective as natural pituitary-gland growth hormone and it also distributes in the body in a similar way to endogenous growth hormone. Mikkelsen made it clear that the Phase II trial also confirmed the positive safety profile of ACP-001, thereby fulfilling patients' and endocrinologists' expectations of such a product. Clinical studies will now be carried out on adults and children suffering from growth hormone deficiency; furthermore, an application for marketing authorization in Europe and the USA is being planned for 2015.

The annual market for human growth hormone is currently 3 billion US dollars, with sales continuing to grow. Biosimilars only occupy around three per cent of this market although the patent for a biopharmaceutically produced first-generation hGH expired several years ago. Per patient treatment costs amount to an average of 20,000 – 25,000 dollars per year. Ascendis Pharma is quite confident about the future although many other pharmaceutical companies are competing with the company for second-generation hGH drugs. However, Ascendis Pharma's proprietary TransCon linker technology is far superior to the strategies used by other pharmaceutical companies for achieving the sustained release of drugs.

Further information:
Ascendis Pharma GmbH
Im Neuenheimer Feld 584
69120 Heidelberg
Tel.: +49 (0)6221-43853 0
Fax: +49 (0)6221-43853 11
E-mail: germanoffice(at)ascendispharma.com

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