

R&D Report

By employing a combination of original in-house research, in-licensing, and product life cycle management (PLCM), Nippon Shinyaku aims to continually enhance its development pipeline and steadily launch new products. Gradually we are seeing the fruits of these efforts, including the launch of Vidaza[®], a remedy for myelodysplastic syndrome (MDS), in March 2011.

Nippon Shinyaku's Research and Development Vision

Nippon Shinyaku's research and development division focuses on the Company's fields of specialty as it strives to supply the market with new products that offer at least one distinctive benefit in terms of efficacy, safety, or patients' quality of life (QOL). Nippon Shinyaku determined five areas of medical specialty on which to focus: urology, hematology, obstetrics and gynecology, otorhinolaryngology, and orthopedics. We work as fast as we possibly can to provide patients with the good news that they can find relief from their suffering. We do this through three avenues: in-house research aimed at developing original medicines, licensing from other companies, and product life cycle management (PLCM).

Vidaza® Product Launch

Development of a Long-Awaited New Drug

Based on a license from Celgene Corporation of the US (New Jersey), we introduced “Vidaza® 100 mg for Injection” to the Japanese market as a treatment for myelodysplastic syndrome (MDS). Vidaza® is an injectable, lyophilized preparation whose active ingredient is azacitidine, a nucleic acid analog. Nippon Shinyaku developed it for the Japanese market and began selling it in March 2011.

MDS is a group of intractable hematological disorders that often progress to leukemia. Major symptoms are general fatigue due to anemia, increased susceptibility to infections due to low white blood cell count (leukocytopenia), and bleeding tendency due to low platelet count. Patients frequently receive blood transfusions as part of their treatment, but this can cause complications including iron overload and multi-organ toxicity. The number of MDS sufferers in Japan is estimated at 9,000. Since no effective treatment was available before Vidaza® appeared on the market, the development of a new treatment was eagerly anticipated.

▶ Drug Discovery Research

The focus of our in-house research is on hematological malignancies and chronic inflammatory diseases. We are developing our original and unique products as speedily as possible, shedding light on the previously unknown causes of diseases.

▶ Licensing-in Activity

We work actively to license in both marketed products and development candidates, in order to enhance our product pipeline.

▶ Product Life Cycle Management (PLCM)

We examine possibilities for adding new indications or new formulations for our products on the market and under development, in order to maximize product value.



Vidaza®'s Potential to Change MDS Treatment

Starting with North America and Europe, Vidaza® is now sold in more than 30 countries around the world. In the United States, it is used as the first-line therapy for MDS. When Vidaza® enters a cell, it is incorporated into the cell's DNA or RNA after being phosphorylated and consequently exerts a cytotoxic effect via inhibition of protein synthesis. It also inhibits DNA hypermethylation which often occurs in MDS tumor cells, resulting in the promotion of normal blood cell development. In overseas clinical trials involving high-risk MDS patients, the median overall survival of patients who received azacitidine was 24.5 months compared with 15.0 months for patients who received conventional treatments. This represents a significant extension of survival, with the two-year survival rate nearly doubled.

By providing the medical field with a new therapeutic agent for MDS, Nippon Shinyaku has given new hope to MDS patients and their families, who until now had suffered greatly in the absence of an effective treatment. We expect that this new treatment will also be a boon to all of the medical professionals involved in MDS treatment.

Development of Selexipag (NS-304)

Selexipag (NS-304) is a new, orally administered prostacyclin (PGI₂) receptor agonist with a non-prostanoid structure. Compared to previous PGI₂ analogues, it remains in the blood longer and has higher selectivity for PGI₂ receptors. In Japan, Phase II clinical trials are underway for indications of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). Overseas, a Phase III clinical trial is underway for PAH.

PAH is a potentially deadly medical condition characterized by increased pressure in the pulmonary arteries, which can lead to heart failure. In Japan, an estimated 10,000 people suffer from PAH. To date, the most effective PAH treatment, generally given to patients with the most severe symptoms, has been intravenous administration of PGI₂. Because this treatment is very risky and burdensome for patients, everyone affected has long awaited the development of a highly effective orally administered treatment that works by the same mechanism. There is hope that in the future, PAH patients may receive three therapeutic agents concurrently from an early stage of their treatment. The three are a phosphodiesterase type 5 inhibitor (PDE5i), endothelin antagonist (ERA), and PGI₂ receptor agonist. Of the three, there has not yet been an orally administered PGI₂-based agent in common use anywhere in the world. We believe that Selexipag will prove to be the answer to this as yet unmet need.

In addition to Selexipag, Nippon Shinyaku has already launched Adcirca®, a tadalafil preparation that is said to be the best of the PDE5i-based treatments for PAH, and we are in the process of developing Macitentan, an ERA. Going forward, Nippon Shinyaku aims to contribute to society by providing groundbreaking combination therapy for PAH using these three agents.

Pipeline

Domestic

Code No.	Generic name	Therapeutic field	Indications	Development	Phase I	Phase II	Phase III	Application	Launch Preparation
NS-315	Tramadol hydrochloride	Inflammation/allergy	Non-cancer related pain	Licensed in from Grünenthal GmbH					
NS-11	Acamprosate	Others	Alcohol dependence	Licensed in from Merck Serono International S.A.					
LY450190	Tadalafil	Urology	Urinary disorder caused by BPH	Licensed in from Eli Lilly Japan K.K.					
NS-304	Selexipag	Cardiovascular	Pulmonary hypertension	Co-development with Actelion					
ACT-064992	Macitentan	Cardiovascular	Pulmonary arterial hypertension	Licensed in from Actelion			Phase III (Preparation)		
NST-141		Inflammation/allergy	Pruritus associated with atopic dermatitis, etc.	Co-development with Taiho Pharmaceutical Co., Ltd.					
NS-24	Tramadol hydrochloride	Inflammation/allergy	Cancer pain Non-cancer related pain	Licensed in from Labopharm Inc.					

Overseas

Code No.	Generic name	Therapeutic field	Indications	Development	Phase I	Phase II	Phase III	Application	Launch Preparation
NM441	Prulifloxacin	Infectious diseases	Synthetic antibacterial	Yuhan Corporation					
				Optimer Pharmaceuticals, Inc.				Application (Preparation)	
				Lee's Pharmaceutical Holdings Limited			Phase III (Preparation)		
NS-304	Selexipag	Cardiovascular	Pulmonary hypertension	Actelion Pharmaceuticals Ltd.					
NS-187	Bafetinib	Hematologic malignancies	B cell chronic lymphocytic leukemia Advanced prostate cancer	CytRx Corporation					
			Chronic myelogenous leukemia			Phase II (Preparation)			
			Glioblastoma multiforme						
NS-018		Hematologic malignancies	Myelofibrosis		Phase II (Preparation)				

New Technologies

Genomic Drug Discovery and Nucleic Acid Drugs

Drug creation by pharmaceutical companies is set to change dramatically in the 21st century. At present, Nippon Shinyaku is actively engaged in advanced research centered on genomic drug discovery and nucleic acid drugs at Drug Discovery Laboratories in Tsukuba, Ibaraki Prefecture. At Discovery Research Laboratories in Kyoto, we focus on specific high-need medical conditions within our fields of specialty and concentrate on developing new therapeutic agents that selectively act on biomolecules related to particular conditions.



Searching for New Drug Seeds

When the human genome was unraveled, researchers were surprised to find that much of the DNA sequence did not code genes governing the production of proteins essential to the functioning of the human body. In fact, as much as 98.5% of the human genome is not concerned with such proteins. On the other hand, codes for functional ribonucleic acids (RNAs), which are closely involved in bodily functions and the onset of disease, were discovered hidden within these so-called “junk DNA” sequences. By understanding the roles of functional RNA, we hope to be able to conquer diseases that have so far been difficult to treat by using existing pharmaceuticals. Nippon Shinyaku collaborates with universities and public research institutes as we search for new drug seeds.



Research and Development of Nucleic Acid Drugs

Nucleic acid drugs act directly on genes that cause diseases, making it possible to treat illnesses that could not previously be cured using traditional low-molecular drugs or antibody drugs. Consequently, there are high hopes for nucleic acid drugs as the next generation of

bio-pharmaceuticals. Before they can be practically applied, however, there are two technological hurdles that must be overcome: the development of methods for synthesizing nucleic acids and for delivering them where they need to go. Nippon Shinyaku has succeeded in the development of an efficient and highly versatile RNA synthesis method that makes it possible to synthesize long-chain RNA linking as many as 50 to 100 nucleotide bases. Nippon Shinyaku was also a frontrunner in researching the delivery of nucleic acid drugs to target sites relevant to particular medical conditions, and we have developed technologies that enable administration of these drugs in ways that are safe for humans. One result of research using our proprietary technologies was that Nippon Shinyaku became the first entity in the world to demonstrate the cancer-controlling effect of small interfering RNA (siRNA) in cancer mouse models. By applying proprietary technologies that we have cultivated over the years, we aim to create unique nucleic acid drugs that will be useful in the treatment of illnesses for which there are as yet no effective remedies.



Nippon Shinyaku's Drug Discovery Laboratories (in Tsukuba, Ibaraki Prefecture) performs advanced research in areas like genomic drug discovery and nucleic acid drugs.