February 26, 2004
AnGes MG, Inc.

Investigational New Drug (IND) application filedwith the US FDA for HGF genetic medicine against ischemic heart disease -Peripheral arterial disease and ischemic heart disease related clinical trials in the USA-

AnGes MG filed an investigational new drug (IND) application for hepatocyte growth factor (HGF) genetic medicine with the Food and Drug Administration (FDA) on February 25, 2004 through its US subsidiary, AnGes Inc. in order to start Phase I study of medicine against ischemic heart disease (IHD).

In the USA, AnGes MG has been conducting Phase II clinical trials for HGF genetic medicine against peripheral arterial disease (PAD) since April 2003. In addition, AnGes MG intends to start conducting IHD related clinical trials in the near future, as a larger number of patients are affected, thereby aiming to launch HGF genetic medicine for both diseases at an early date.

HGF genetic medicine has a neovascular effect and is intended to cure ischemic disease in which the lumenblood vessels narrows due to arteriosclerosis and the blood flow is impaired. As this medicine's effect differ from that of other conventional drugs, it is expected to be effective for patients who do not sufficiently respond to conventional drug therapy or who cannot undergo surgery. AnGes MG has been developing this medicine in fields centering around PAD, where the blood circulation in the lower limbs is decreases (obstructive arteriosclerosis and Buerger's disease), and IHD, in which the blood flow in the heart is impaired.

The objective of the current IND application is to start the Phase I clinical trial of HGF genetic medicine in the field of ischemic heart disease in the USA. Generally, the Phase I clinical trials are conducted to verify safety and healthy volunteers are used as subjects. However, in this development project of HGF genetic medicine for ischemic heart disease, AnGes MG is going to administer the medicine to a limited number of patients with severe ischemic heart disease using a catheter for direct administration of the medicine to the ischemic lesions, beginning with the Phase I trial. This is for the purpose of verifying the

safety as well as the efficacy of the medicine. Since the IND application for starting the Phase I clinical trial for IHD in the USA, AnGes MG has been preparing for the start of clinical trials related to the same diseases in Japan during 2004.

In addition to the PAD related Phase II clinical study of HGF genetic medicine now underway in the USA, AnGes MG is going to begin PAD related multi-center double blind Phase III clinical trials soon in Japan. With the IND application for HGF medicine to treat IHD, AnGes MG aims to concurrently develop this medicine for use against both PAD and IHD in Japan and the USA.

AnGes MG has granted Daiichi Pharmaceutical Co., Ltd. the distribution rights for HGF genetic medicine in both the PAD and IHD fields in Japan, the US and Europe.

Reference

Specific therapeutic significance of the HGF genetic medicine
It is known that HGF has a strong vascularization effect; the present pharmaceutical agent deposits a gene to produce HGF in sites of vascular necrosis, thus the HGF protein is generated locally, resulting in blood vessel regeneration to improve the (arteriosclerotic) condition - the first genetic medication to be produced in Japan. The agent thus developed does not employ a virus vector to introduce the genetic sequence to a patient's DNA - it is a pure, "naked" DNA sequence, so negative effects that usually accompany a DNA sequence introduction with a virus vector do not appear here. In addition, since the present medicine alters the condition of necrosis by regenerating the blood vessels, as opposed to all conventional pharmaceutical agents, positive results can be expected in cases when conventional therapy for PAD and IHD fails, or is increasingly complicated.

Explanation of specialized terms
1. Gene medicine
A medicine, wholly, or partially comprising a genetic expression.

2. Hepatocyte Growth Factor (HGF)
A growth factor developed from hepatocytes; in addition to blood vessel regeneration, it initiates various processes necessary for tissue / organ regeneration during organ formation

(organogenesis).

3. Peripheral arterial disease (PAD)

Since peripheral blood vessels of the four limbs can become clogged, so that the supply of blood to muscle and skin tissues is not adversely affected, causing the following symptoms: a feeling of paralysis, coldness, arrest of blood flow (intermittent claudication), ulcer of lower limbs (thrombic disease), pain even when there is no motion. A condition characteristic of arteriosclerosis obliterans (ASO), Buerger's disease. There are approximately 100,000 patients in Japan and 1,000,000 - in the U.S.A.

4. Ischemic heart disease (IHD)

Vessels supplying the heart (coronary blood vessels) become contracted (or constricted) to a certain extent resulting in insufficient blood flow after physical activity; characteristic symptoms are angina pectoris accompanied with a tightness in the chest and chest pains, and myocardial infarction causes by disorders of coronary blood vessels becoming completely clogged - heart muscle tissue becoming ischemic. There are approximately 100,000 patients in Japan who underwent angioplasty surgery due to severe heart disease, and 1.8 million - in the U.S.

5. Naked DNA

For a genetic expression to work properly, genes have to enter a cell; in conventional practice, however, genes may only come as close as to be attached to the cell membrane, unable to penetrate it. A carrier, an agent to introduce the genetic expression to a cell, becomes necessary at this point. An improved virus vector (i.e., purified not to pose danger to the host cell) is usually used for these purposes, and the method features a genetic expression introduced to a cell by a ribosome. Our methodology of the HGF genetic medication, by contrast, has genes spiraling in "plasmid DNA" (a naked DNA technology). Plasmid DNA alone may not be able to penetrate the cell membrane, it can, however, generate genes if injected intra-muscularly. The technology is extremely safe with no danger of contamination and cytotoxicity due to ribosomes or viruses.