AnGes

About the September 7, 2022 Announcements

— Leading Global in Gene medicine —

AnGes

September 2022

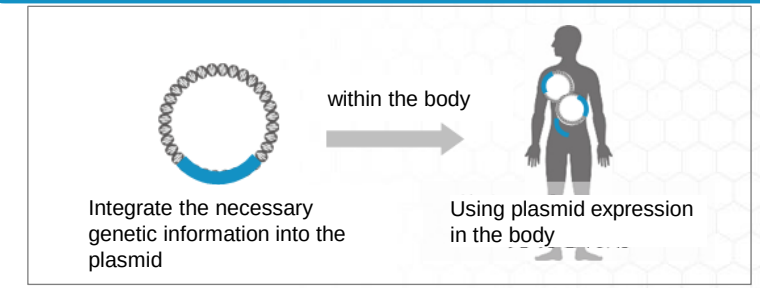
01

About COVID-19 DNA Vaccine

Background to Development

We decided to use the technology cultivated in R&D of our world-first gene therapy product using plasmid DNA to develop a COVID-19 DNA vaccine.

Experience of developing and commercializing HGF gene therapy product



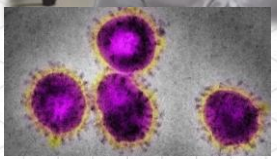
The insertion of a gene into a circular DNA molecule called a plasmid that is found in bacteria such as E. coli and the administration of this plasmid DNA causes the production of proteins the body needs

A large amount of plasmid DNA can be cultivated through introduction into E-coli bacteria, enabling rapid large-scale plasmid production

Plasmid DNA technology cultivated in gene therapy product

Development of COVID-19 DNA Vaccine

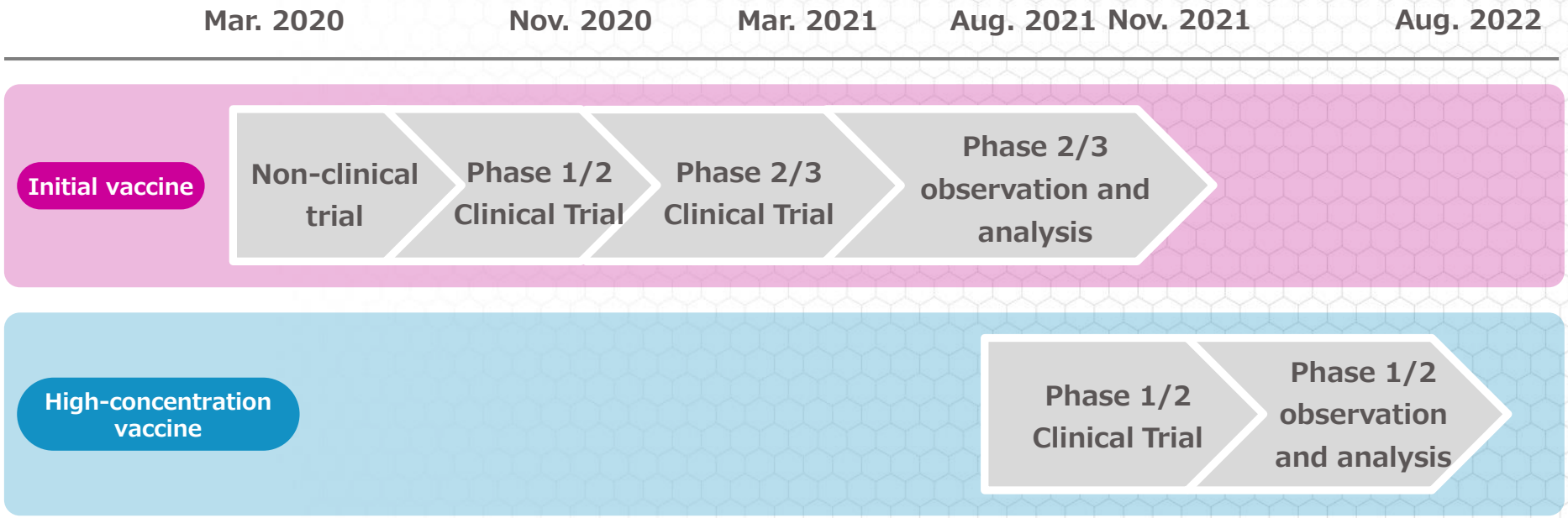
Research at Osaka University



Source: WHO website

Progress of Development

After deciding to develop a DNA vaccine for the original Wuhan strain of COVID-19, we began conducting a non-clinical trial for the initial vaccine from March 2020 and completed administration for a Phase 2/3 Clinical Trial by March 2021
Since August 2021, we have also been conducting a Phase 1/2 Clinical Trial using a vaccine with a higher drug concentration than the initial vaccine



Clinical Trial Results and Future Plans

Previous DNA vaccine

Safety	Immunogenicity
◎	△

Discontinued development of previous DNA vaccine and started research into improved DNA vaccine

Improved DNA vaccine

Review of platform

Improvement of plasmid expression efficiency and transfer efficiency

Formulation for intranasal delivery

Stimulate a broad immune response to prevent viral replication and spread

Initiative with Stanford University

Utilization of Stanford University's "Gold-Nanostar Octopod" Technology

At Stanford University, progress is being made on research into an intranasal formulation of the vaccine which will induce a broader immune response, potentially preventing multiplication of the virus and impeding its spread with respect to viral lung diseases.

An intranasal formulation of the vaccine was prepared using plasmid DNA with the genome sequence of the original Wuhan strain, and an experiment using mice confirmed a surge in serum antibodies (IgG, IgA, and IgM). The intranasal formulation was found to demonstrate neutralizing activity not only against the Wuhan strain but also against variants such as the β variant and histological analyses revealed cellular and humoral immune responses against the spike protein in the lymph nodes and spleen.

Based on these findings, we will start development to prepare a formulation for intranasal delivery based on the latest variants.

■ Outline of Sponsored Research Agreement

Name	Stanford University
Location	California, USA
Research period	Approx. 3 years
Research expenditure	Approx. 3 million USD

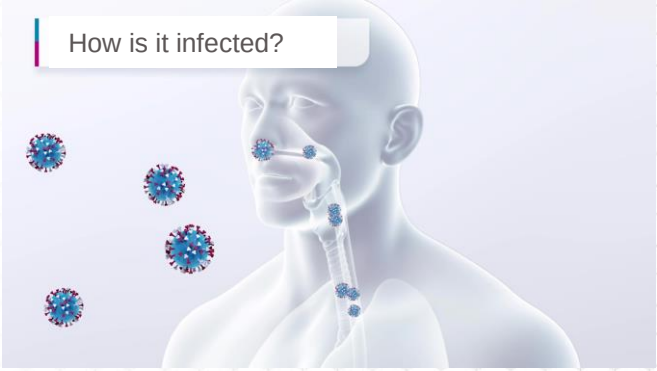
Details of Development of Improved Vaccine

R&D of intranasal formulation for a safe, highly effective vaccine

[What is intranasal delivery?]

The viruses and bacteria which cause respiratory diseases such as COVID-19, influenza and the common cold enter the body through the mucosal membranes of the "upper respiratory tract" (nose, mouth and throat) and the "gastrointestinal tract" (intestine, etc.).

The upper respiratory and gastrointestinal tracts have a mucosal immune system, which attacks viruses to protect the body from infection.



Production of IgA antibodies (a type of antibody secreted into mucosal membranes) in the nose and throat may help prevent infection itself and intranasal delivery could create immunity in the part of the respiratory tract that is the site of infection.

02

HGF Gene Therapy Product

Development Status of HGF Gene Therapy Product

In March 2019, we obtained marketing approval with conditions and time limit in Japan, claiming improvement of lower limb ischemic ulcers in patients suffering from chronic arterial occlusion as the efficacy, effect, or performance

Phase 3 Clinical Trial for approval of the additional indication of chronic arterial occlusive disease with rest pain in Japan
Phase 2 Clinical Trial in the US for arteriosclerosis obliterans with lower limb ulcer in patients with chronic arterial occlusion

■ Conditional and time-limited approval system

Project (Nonproprietary name)	Area	Indications	Basic research	Non-clinical trial	Clinical trial		Approval/review	Conditional /time-limited approval	Sale	Post-marketing surveillance	Formal approval
					Phase 1	Phase 2					
HGF gene therapy product (Beperminogene perplasmid)	Japan	Ulcer associated with chronic arterial occlusive diseases						Approved	On sale	On going	

■ Standard approval system

Project	Area	Indications	Basic research	Non-clinical trial	Clinical trial			Approval/review	Approval
					Phase 1	Phase 2	Phase 3		
HGF gene therapy product (Beperminogene perplasmid)	Japan	Chronic arterial occlusive diseases Rest pain					On going		
	United States	Ulcer associated with chronic arterial occlusive diseases				P2b (On going)			

Summary of Results of Trial for Rest Pain

The results of the Phase 3 Clinical Trial of the HGF gene therapy product for the additional indication of chronic arterial occlusive disease with rest pain showed that we failed to meet the primary endpoints for rest pain

■ Conditional and time-limited approval system

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Discontinuation of development

Future Plans

We will push ahead as planned with **preparations to apply to obtain the approval** of the HGF gene therapy product **in Japan**, with improvement of lower limb ischemic ulcers in patients suffering from chronic arterial occlusion as the stated efficacy, effect, or performance.

We will in **the US** of the HGF gene therapy product for the treatment of lower limb i**continue with the Phase 2 Clinical Trial** schemic ulcers in patients with chronic arterial occlusion and push ahead with development aiming to quickly progress through the clinical trial stages.

■ Conditional and time-limited approval system

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					Phase 1	Phase 2					
HGF gene therapy product (Beperminogene perplasmid)	Japan	Ulcer associated with chronic arterial occlusive diseases						Approved	On sale	On going	Application being prepared

Continued implementation

■ Standard approval system

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HGF gene therapy product (Beperminogene perplasmid)	Japan	Chronic arterial occlusive diseases Rest pain						Discontinuation of development	
	United States	Ulcer associated with chronic arterial occlusive diseases				P2b (On going)		Continued implementation	

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AnGes's website
https://www.anges.co.jp/en/