NOVOTECH™
The Asia Pacific CRO

CLINICAL TRIAL LANDSCAPE OF CYSTIC FIBROSIS IN ASIA-PACIFIC

CONTENTS

3 EPIDEMIOLOGY OVERVIEW

4 STANDARD OF CARE

5 CLINICAL TRIAL LANDSCAPE

6 KEY OPINION LEADERS IN CYSTIC FIBROSIS

8 NOVOTECH OVERVIEW

EPIDEMIOLOGY OVERVIEW

Background

Cystic fibrosis is a rare autosomal recessive disease which primarily affects the lungs and digestive system due to a malfunction in the exocrine system responsible for producing saliva, sweat, tears and mucus. The specific mutation for cystic fibrosis is found on chromosome 7 (7q31) and is known as the 'cystic fibrosis transmembrane conductance regulator' (CFTR) gene. The CFTR gene helps move salt in and out of the cells. In cystic fibrosis, the movement of salt doesn't happen properly, leading to the presence of an abnormal amount of excessively thick and sticky mucus within the lungs, airways, and the digestive system. This leads to impaired digestive functions of the pancreas and traps bacteria in the lungs causing recurrent infections, which eventually cause an irreversible lung failure, which is the major cause of death in patients [1].

At least 1,700 mutations of the CFTR gene have been found till date. From birth, a person diagnosed with the disease requires intensive daily physiotherapy to clear the lungs and airways, countless medications, and frequent hospitalisations, as there is currently no cure for cystic fibrosis [2].

Disease Prevalence

It is estimated that about 70,000 to 100,000 people are suffering from cystic fibrosis globally, but the incidence of the disease varies greatly across the globe. Cystic fibrosis occurs equally in males and females [3].

Cystic fibrosis is one of the most frequently diagnosed disorders in Caucasian populations, with an incidence of 1 in every 2,000 to 3,000 births [4].

About 3,500 people are living with cystic fibrosis in Australia and 1 in 25 people carry the recessive cystic fibrosis gene change. In Tasmania, one of Australia's states, 1 in 20 people carry the cystic fibrosis gene, which is the second highest rate in the world. Likewise, in New Zealand, cystic fibrosis is the most common life-threatening inherited disorder with approximately 1 in 25 people carrying the cystic fibrosis gene [5].

In Asia, the prevalence varies but some studies have found it to be as high as 1 in 10,000 people. Although cystic fibrosis appears to be less frequent amongst Asian ethnicities, it's lower prevalence can be attributable to under-diagnosis and to the lack of centralized patient registries. However, many countries in the region are creating local patient registries and establishing more frequent diagnosis [6].
In China, it is estimated that about 20,000 people live with cystic fibrosis [7], while in India it is estimated about 3,000 children are born with the disease each year [8].

STANDARD OF CARE

The table below summarizes the current and emerging treatment options for cystic fibrosis [9].

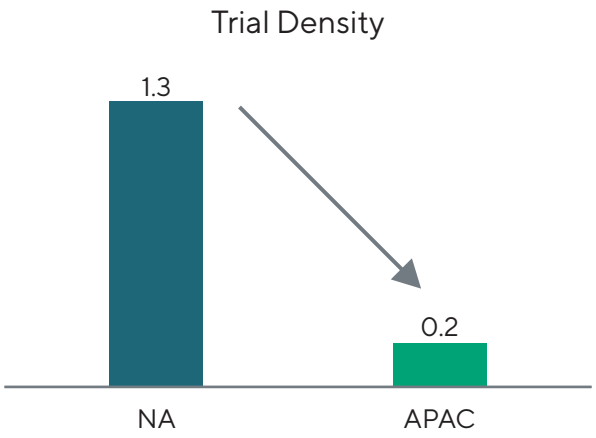
Treatment options	• Antibiotics (e.g. tobramycin) • Inhaled enzymes (e.g. Pulmozyme) • Insulin to manage diabetes • Inhalers to open up the airways • Steroids to help reduce swelling within the airways • Physiotherapy and postural drainage of the chest • Diet tailored to patient needs – often a special diet that is high in protein and calories is needed • Pancreatic enzymes to help absorb fats and protein • Vitamin supplements, especially vitamins A, D, E and K • Nasal steroids for, or surgical removal of, nasal polyps
Potentiators	Drugs that help open the CFTR channel at the cell surface and increase chloride transport, e.g. ivacaftor.
Correctors	Drugs that help the defective CFTR protein fold properly so that it can move to the cell surface e.g. lumacaftor, tezacaftor.
Read-through compounds/ Amplifiers	Aim to allow full-length CFTR protein to be made, even when the RNA contains a mutation telling the ribosome to stop. Amplifiers increase the amount of CFTR protein that each cell makes. This would be helpful for people with cystic fibrosis who don't make enough of the CFTR protein. Amplifiers are not yet on the market and are in phase 2 drug trials.
Triple combination drugs	A combination of elexacaftor, tezacaftor, and ivacaftor for those with the most common mutation, F508del, and recommended for those aged 6 years and older. Elexacaftor and tezacaftor are CFTR correctors, while ivacaftor is a potentiator.
RNA therapies	To either fix the incorrect instructions in defective RNA or provide normal RNA directly to the cell.
Gene-editing techniques	To repair the underlying genetic defect in the cystic fibrosis gene DNA.
Gene replacement techniques	To provide a correct copy of the cystic fibrosis gene.
Next-generation CFTR modulators	To eliminate or improve the defective folding of the protein as well as to improve the surface stability and chloride channel function in cells with CFTR mutations that cause cystic fibrosis symptoms.

CLINICAL TRIAL LANDSCAPE

About 100 industry-sponsored clinical trials in cystic fibrosis are currently ongoing or planned, about a fourth of which involve the Asia Pacific region. Clinical trials in Asia-Pacific predominantly involve Australia and New Zealand, but also involve sites in India and China as well.

Due to its large population and lower volume of studies, the Asia-Pacific (APAC) region has lower competing trial risk with a trial density about 6 times lower than North America (figure 1).

Figure 1. Comparison of the trial density* for industry-sponsored cystic fibrosis clinical trials in North America and Asia-Pacific [10]



**Trial density is the number of recruiting sites for industry-initiated trials per million urban population*

Trials running in the Asia-Pacific region show recruitment durations about 40% shorter than trials in North America (figure 2). In addition, studies ongoing in the Asia-Pacific region have a higher median patient recruitment rate compared to North America (0.7 and 0.4 patient per site per month respectively) (figure 3).

Figure 2. Comparison of the median patient enrolment duration (in months) for cystic fibrosis clinical trials in North America and Asia-Pacific [10]

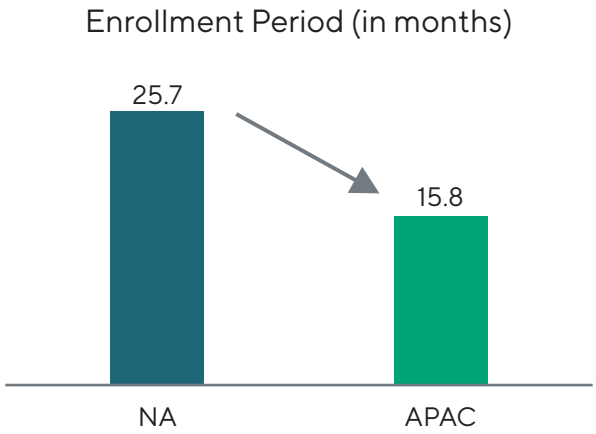
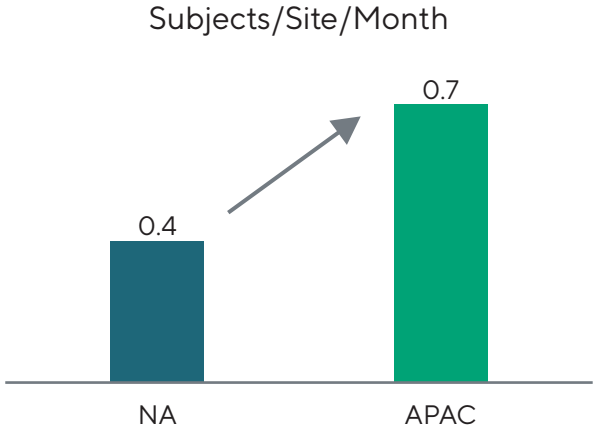


Figure 3. Comparison of the median patient recruitment rate (in subjects per site per month) for cystic fibrosis clinical trials in North America and Asia-Pacific [10]



KEY OPINION LEADERS IN CYSTIC FIBROSIS

Prof. Claire E Wainwright
University of Queensland - AUSTRALIA

Professor Wainwright is a Paediatric Respiratory Physician and co-lead for cystic fibrosis services at the Queensland Children's Hospital. Her research focuses on airway microbiology, paediatric respiratory infections and early lung disease in cystic fibrosis, ataxia telangiectasia along with the clinical management of bronchiolitis and asthma. In 2018, Professor Wainwright was awarded a Member of the Order of Australia (AM) for leadership into the study of cystic fibrosis.

A/Prof. Philip J Robinson
The Royal Children's Hospital - AUSTRALIA

A/Prof. Philip Robinson has been involved in paediatric respiratory research for more than 25 years including many innovative multi-centre drug trials as well as individually designed and led projects involving cystic fibrosis and primary ciliary dyskinesia (PCD). His main area of interest is in suppurative lung disease with particular interest in cystic fibrosis and PCD. In the past four years his team has been involved in 10 multicentre drug trials in cystic fibrosis including trials of the new mutational specific drug, Ivacaftor.

Prof. Barry Clements
UWA Medical School, Paediatrics - AUSTRALIA

Professor Clements has been a Clinical Consultant in Respiratory Medicine at Perth Children's Hospital for over 30 years. His interest in research has been on improving inhalation therapy in cystic fibrosis patients for which he has recently received funding for two large international projects. In 2018, he founded Respirion Pharmaceuticals, an early-stage biotechnology spinout from the Telethon Kids Institute in Perth. Respirion's lead product, an inhaled therapy for cystic fibrosis is being developed in both Australia and in the US.

Prof. Scott Bell
The Prince Charles Hospital - AUSTRALIA

Professor Bell is a Senior Physician of the Adult Cystic Fibrosis Centre at The Prince Charles Hospital with over 300 patients. He leads the Lung Bacteria Laboratory at QIMR Berghofer Medical Research Institute in Brisbane and has a long history of supporting multi-disciplinary research. His research interests include the cystic fibrosis microbiology and acquisition pathways for human infection.

Prof. Kunling Shen
Beijing Children's Hospital – CHINA

Professor Shen is the Chief of China National Clinical Research Center for Respiratory Diseases, Beijing Children's Hospital. She is specialized in respiratory, virology and sleep medicine. She has carried out numerous projects and studies in respiratory, virology and sleep medicine in addition to publishing nearly one hundred papers and books on the above topics.

Prof. Zhe Zhang
Peking University – CHINA

Dr. Zhang's work on the cystic fibrosis transmembrane conductance regulator (CFTR) has helped deepen the mechanistic understanding of ligand-gated ion channels and has enormous potential for helping people suffering from cystic fibrosis. Dr Zhang is now working as a Principal Investigator (PI) in the School of Life Sciences to establish the Lab of Membrane Biology and Biophysics.

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For more information, visit https://novotech-holdings.com/

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