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WHY IS SWEAT CHLORIDE IMPORTANT IN CYSTIC FIBROSIS?

Vertex's goal is to discover and develop medicines that target the underlying cause of cystic fibrosis (CF) and help restore cystic fibrosis transmembrane conductance regulator (CFTR) function for people with CF to normal levels. Lung function, as measured by percent predicted forced expiratory volume ($ppFEV_1$), is an important endpoint in clinical trials as lung disease is the main cause of morbidity and mortality in people with CF. Specifically, $ppFEV_1$ is an important prognostic marker for people with CF and $ppFEV_1$ is an accepted regulatory endpoint for CF drug development. Therefore, as CFTR modulators are evaluated in clinical trials, it is fundamental to show either an improvement or non-inferiority in lung function compared to standard of care.

CF, however, is a multi-system disease caused by CFTR dysfunction, and while greater restoration of CFTR function as measured by sweat chloride (SwCl) concentration may be achieved through drug development, additional improvements in lung function, as measured by $ppFEV_1$, may not be possible. Thus, SwCl, a systemic, sensitive and reliable measure of CFTR function, could allow differentiation between highly effective CFTR modulators once lung function improvement, as measured by $ppFEV_1$, has been maximized. Since SwCl has been used as a diagnostic test for CF, thresholds have been established and can be used as potential therapeutic targets.

The diagnostic threshold for SwCl in CF is 60 mmol/L, and it is known from pre-CFTR modulators era natural history studies that SwCl values below 60 mmol/L are generally associated with improved outcomes such as better and more stable lung function, better nutritional status and improved survival. SwCl levels below 30 mmol/L are typically seen in healthy individuals, without signs or symptoms of CF.

Vertex's ambition is to move beyond the historical focus on $ppFEV_1$ to a broader, more aspirational goal to continue to improve CFTR function overall and to help restore CFTR function to levels that are not associated with disease, as measured by SwCl. This may potentially lead to greater systemic benefit for people with CF.