# 2. SYNOPSIS: INVESTIGATIONAL PLAN

| | |
|---|---|
| **Protocol No.** | CFFC-OB-11 |
| **Title** | A Long-Term Prospective Observational Safety Study of the Incidence of and Risk Factors for Fibrosing Colonopathy in US Patients with Cystic Fibrosis Treated with Pancreatic Enzyme Replacement Therapy: A Harmonized Protocol Across Sponsors |
| **Rationale** | The US Food and Drug Administration has mandated post-marketing requirements for the use of pancreatic enzyme replacement therapy (PERT) for the treatment of exocrine pancreatic insufficiency, including a 10-year, observational study to prospectively evaluate the incidence of fibrosing colonopathy (FC) in patients with cystic fibrosis (CF) and to assess potential risk factors for the event. |
| **Study Period** | |
| First Patient Encounter | 31 July 2012 |
| Close of Enrollment into the Base Study Population | 30 July 2014 |
| End of patient follow-up | 10 April 2020 |
| **Study Design** | Prospective, observational, population-based cohort study conducted in patients with a diagnosis of CF enrolled in Cystic Fibrosis Foundation Patient Registry (Port CF) and treated at sites with Institutional Review Board (IRB) approval for the study. Routinely collected data (i.e., such as those collected in the standard Port CF data collection form) are used to determine exposure to specific PERT and potential risk factors for the study outcome. Patients with suspected FC during the study period are approached by their clinical care team to obtain informed consent for collection of additional data (i.e., outside the standard Port CF data collection form) to augment surveillance and confirmation of FC diagnosis via an independent adjudication committee (see Appendix V for the adjudication committee charter). For additional details, see Figure 6–1 and the protocol (Appendix III). |
| **Main Inclusion Criteria for the Base Study Population** | Enrolled in Port CF<br>Diagnosis of CF<br>Receiving medical care from a Cystic Fibrosis Foundation (CFF)-accredited care center providing data to Port CF with IRB approval for this study |
| **Centers** | 125 US centers |
| **Treatment** | The study did not provide or recommend any treatment. All direction for medication usage was solely at the discretion of the patient's physician in accordance with his/her usual practice. |

| | |
|---|---|
| **Objectives** | **Primary Objective:**<br>The primary objective of this study was to quantify over a 10-year period the incidence of FC in US patients with CF treated with PERT.<br>**Secondary Objective:**<br>The secondary objective of this study was to quantify the association between potential risk factors and the development of FC in patients with CF. |
| **Statistical Methods** | Incidence analyses of FC for the final report were conducted within the entire Base Study Population (defined below). FC events that occurred during concurrent use of specific PERT were of primary interest. However, this study also analyzed FC events that occurred in other person-time categories of exposure (such as exposure to other PERT, or non-exposure to PERT). This analysis accounted for drug switching and temporary or permanent discontinuation by categorizing person-time exposed and unexposed to each specific PERT. Additionally, an overall PERT incidence analysis was performed accounting for patient exposure to any PERT. |
| **Base Study Population** | This prospective observational study was conducted in patients with CF, treated in clinical practice, and enrolled in Port CF. The number of patients prospectively observed for this study was determined by the number of patients enrolled in Port CF, including those who were treated with PERT during the study period.<br>The Base Study Population included all patients enrolled in Port CF who had a diagnosis of CF, were treated at sites with IRB approval for the study, and who had their first on-study encounter in the Port CF registry ('Study Day 1') during the 2-year period starting with the first qualified patient in Port CF (Study Day 1) at the first study clinical site (31 July 2012) and ending with the close of the entry period for the Base Study Population (30 July 2014) (N = 26,025). |

| | |
|---|---|
| **Results** | Over the study period, among the enrolled 26,025 patients, 29 CF patients were suspected to have FC; 3 were confirmed to have FC by the adjudication committee; 22 patients were not confirmed to have FC; and 4 patients were indeterminate. In this study, 22,161 patients were exposed to any PERT on or after their Day 1/study entry and throughout the study period (maximum follow-up time: 7.8 years). Their mean current PERT use time was 5.583 person-years, and their mean combined current and former PERT use time was 5.828 person-years. The mean average daily dose of any PERT was 8,328 lipase units/kg/day and the mean cumulative dose was 17.39 million lipase units/kg. The corresponding incidence rates per 1,000 person-years exposed for confirmed FC were 0.0242 (95% CI [0.0050, 0.0709]) for current use and 0.0232 (95% CI [0.0048, 0.0679]) for combined current and former use. There were no confirmed cases of FC during nonuse time.<br>With only 3 cases of FC confirmed, there were too few events to enable a meaningful analysis of risk factors for FC among patients with CF. |
| **Conclusions** | In this prospective FC study, the observed cumulative incidence rate of FC in patients exposed to PERT was 0.0242 patients per 1,000 person-years, which is 8-fold lower than the expected incidence of 0.17 per 1,000 person-years based on prior studies. The expected number of cases predicted at study initiation was 3 cases per year, and 24 cases over 8 years; however, only 3 cases were observed over almost 8 years of observation.<br>In conclusion, fibrosing colonopathy remains a rare yet serious GI complication of PERT seen almost exclusively in patients diagnosed with CF. This study was a large, prospective cohort study that included most of the patients with CF in the United States and had rigorous adjudication of the suspected FC events. After almost 8 years of observation, this study has demonstrated that the incidence of fibrosing colonopathy in patients with CF in the era of the current treatment guidelines is very low and the incidence has been estimated with high precision. |
| **Study Management** | This study was managed by Cystic Fibrosis Foundation Therapeutics (CFFT) and conducted within the CFF-accredited care center network with guidance, input, review, and approval by the sponsors, including development of materials; recruitment, training and management of sites; and data management and analysis. An independent adjudication committee was formed to validate the diagnosis of FC based on a prospective case definition and decision rules. The CFFT identified the panel of experts and mediated the adjudication process.<br>This analysis for the final study report was performed by IQVIA using SAS version 9.4. |