

THE CHANGING ENVIRONMENT OF ENROLLING CLINICAL STUDIES WITH INHALED ANTIBIOTICS IN CYSTIC FIBROSIS

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Objective: The development of new inhaled antibiotics for use in Cystic Fibrosis pulmonary infections has become a key part of the therapeutic progress and outcome in CF. With multiple new inhaled antibiotics in development, it has become increasingly difficult to enroll such studies. The objective of this research is to quantify the enrollment times over time, identify differences between countries and continents, and describe the various contributing factors influencing enrollment rates.

Methods: Public data (www.clinicaltrials.gov) were reviewed for inhaled antibiotics in CF, for Phase 1 through Phase 4 studies, and enrollment rates calculated (patients/site/month) for various Phases, countries, and types of studies. Data was obtained from amikacin, aztreonam, PA antibodies, tobramycin, fosfomycin/tobramycin combination trials. Telephonic interviews were conducted with investigators and study conduct personnel in Australia, Europe, and the US. Factors such as enrollment criteria, patient age group, size and Phase of study, and competing academic and corrector studies were investigated. A total of 14 studies were reviewed, with 12 providing sufficient public information.

Data: Overall study enrollment has slowed over the last decade, as more programs are underway. Study enrollment substantially depends on the target patient group and inclusion/exclusion criteria. Phase 1 (n=5; 0.19-1.92 pts/month/site, avg 1.14) and Phase 2 (n=4; 0.11-1.92 pts/month/site, avg 0.65), are typically smaller studies, and enroll more rapidly than Phase 3 and Phase 4 studies (n=3; 0.14-0.27 pts/month/site, avg 0.18). Multiple programs start with Phase 1 studies in Australia or Europe, prior to conducting Phase 2 studies in the US, as local regulatory environments allow for a more rapid conduct. Eastern European countries increasingly participate on study conduct, particularly when maximal standard of care is not required. Later stage studies, worldwide, have recently seen slower enrollment due to large approval studies with oral correctors/potentiators. Smaller trials in single countries often demonstrate more rapid enrollment than multinational Phase 3 studies. Patient participation is often a function of the unmet medical need, along with the perceived value of the new therapy, and whether a previously untreated pathogen (e.g. non Pseudomonas) is being targeted.

Conclusions: Timely and successful drug development of inhaled antibiotics for CF will continue to depend on adapting to a changing environment for finding participating subjects. This observation demonstrates a number of alternative strategies to conduct such studies, and may help design trials that are meaningful to patients, answer important questions, and bring novel therapies to CF patients.