



TDN Compound Evaluation Process

Assessment of Candidate CFTR Modulator Agents for Cystic Fibrosis

Concurrent development of CFTR modulators has created tremendous opportunities for new cystic fibrosis therapies. These advances have also led to real concerns that the availability of individuals with CF to participate in clinical trials may soon become a limiting factor in drug development.

To utilize patient resources optimally, the Therapeutic Development Network's Clinical Research Executive Committee and Protocol Review Committee are implementing an early step in clinical protocol evaluation that will apply to agents specifically designed to modulate CFTR ion activity, either by increasing the number of CFTR channels residing at the plasma membrane or by potentiating ion movement through CFTR, or both.

The goal of this evaluation is to independently assess the preclinical biological characteristics to better predict the likelihood of success of each new chemical entity within the class of compounds designated as CFTR modulators.

Several factors will be considered when assessing a compound's likelihood of clinical benefit including, but not necessarily limited to, the following:

1. Mechanism of action (if known) and its novelty relative to other modulator agents.
2. Intention for use as a single agent or in combination with other CFTR modulators.
3. Extent to which compounds have been evaluated in appropriate in vitro model systems including, but not limited to, stable cell lines and primary human bronchial epithelial cells (including number of patient codes tested) under defined culture and assay conditions.
4. Evaluation in animal models, intact tissues or humans (if available).
5. Level of CFTR functional restoration achieved in relevant model systems, expressed either as fractional wild-type CFTR activity or, preferably, in direct comparison to other established modulator agents.
6. Biochemical assessment of CFTR correction in relevant model systems including, but not limited to, stable cell lines and primary human bronchial airway cells.
7. Potential additivity and/or synergy with other modulator agents.
8. Level of CFTR modulation obtained following acute and chronic exposure.

9. Additional data regarding CFTR modulation with potential relevance to clinical benefit.

Please note that compound evaluation will take into account the overall profile of multiple criteria, recognizing difficulties in direct translation to clinical benefit. We also recognize that the mechanism of action of a given compound may influence the relative importance of certain criteria listed above.

The goal, therefore, is to assess overall data that supports the biological basis for CFTR modulation. For this purpose, evaluations will be performed by multiple independent experts under conditions of confidentiality.

The content of these evaluations, along with other aspects of the protocol review process, will be used by the Clinical Research Executive Committee and Protocol Review Committee to score each protocol.

These scores will be provided to TDN sites to allow them to make educated decisions about which studies to select for participation. The ultimate goal is to achieve the most efficient use of TDN centers and resources.

For more information, please write to the TDN Coordinating Center at TDNCC@seattlechildrens.org