



TDN Compound Evaluation Process

Assessment of Candidate Epithelial Sodium Channel Inhibitors for Cystic Fibrosis

The development of epithelial sodium channel (ENaC) inhibitors and other new agents has created significant opportunities for new CF 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 Therapeutics 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 epithelial sodium channel activity.

The goal is to independently assess the preclinical biological characteristics to better predict the likelihood of success of each compound within the class of compounds designated as epithelial sodium channel modulators.

Several factors will be considered when assigning a compound priority score including, but not necessarily limited to, the following:

1. Demonstration that agent blocks ENaC channels, drug potency and whether blockade is reversible. This will typically entail use of bronchial epithelia (ideally primary cells, but cell lines acceptable) in Ussing chamber studies. Patch clamp studies can be useful as supplementary information but are not essential.
2. Demonstration that agent restores airway surface liquid (ASL) volume and/or mucociliary clearance (MCC) in CF human airway epithelial cells. Primary endpoints may include one or both of the following:
 - ASL volume using confocal microscopy or other technologies, utilizing air-liquid interface cultures, where any added ASL volume (if added with drug) and drug concentrations are clinically relevant. The duration of this effect, via serial monitoring of ASL volume, will also be considered.
 - MCC in primary CF human airway epithelial monolayers using imaging methods, ideally in the absence and presence of CFTR modulators.
3. Evaluation of MCC in animal models using clinically relevant doses. Sheep MCC or guinea pig tracheal mucus velocity measurements are typical models.

4. Extent of preclinical safety/toxicity studies, customized for this class of drug. In addition to standard assays, the effect on plasma potassium, aldosterone/renin levels, urine electrolytes (Na/K ratio) and adrenal medullary histology are of highest priority.
5. Early human clinical experience, if available. If conducted, the effect on 24-hour urine collections for aldosterone, urine Na/K ratio; plasma potassium levels, and urine PK of drug (aligned with serum and urine electrolyte assays) are of highest priority.

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 ENaC inhibition. 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 TDN's 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.