Prolonged Cardiac Repolarization in Dravet and Lennox-gastaut Syndromes

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Rationale:

People with epilepsy are at an increased risk of arrhythmias and sudden cardiac death. Rare intractable forms of epilepsy such as Dravet (DS) and Lennox-Gastaut syndromes (LGS) are associated with a high risk of sudden unexpected death in epilepsy (SUDEP, e.g. DS: 9.32 cases per 1000 people/year). Almost all people with DS have *de novo* variants in sodium channel genes *SCN1A* or *SCN1B* that are also expressed in the heart. LGS is not associated with specific genetic variants. Preclinical models of DS exhibit altered cardiac electrical function. We hypothesize that people with intractable forms of epilepsy exhibit a higher prevalence cardiac electrical abnormalities than the general population.

Methods:

Using 12-lead ECG recordings, we evaluated the cardiac electrical activation-recovery interval (QTc duration). The study includes baseline/pre-drug 12-lead ECGs from a large cohort of people with DS (n=194) and LGS (n=396) who were screened for eligibility in the GW-Pharma/Jazz Epidiolex clinical trials. Additionally, we performed ECG analysis on 12-lead ECGs from 69 people with DS in Australia.

Results:

Building on our previous results from ambulatory and epilepsy monitoring unit EEG/ECG recordings, results from standard 12-lead ECGs confirm that large subsets of people with DS (16.7%, 44/263) and LGS (13.1%, 52/396) have clinically defined QTc prolongation. Females with DS have the highest prevalence of QTc prolongation (18.6%, 19/102). The

prevalence of QTc prolongation in the DS and LGS groups is larger than the general population (8.7%, $p < 0.001$), pediatric population (0.03-0.1%, $p < 0.001$), and people with congenital Long QT Syndrome (0.05%, $p < 0.001$).