Evaluating the Arrhythmic Potential of Vanoxerine in Human iPSC Derived Cardiomyocytes on a Multiwell MEA.

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Methods
- MEA Results
  - 48-well MEA plates were pre-coated with 5µl of fibronectin directly over the electrode grid and incubated at 37°C one hour before plating cells.
  - 100nM and 316nM Vanoxerine also causes a significant lengthening of the FPD to a lesser degree with a further lengthening of the beat period. There is a further increase in the amplitude and slope.
  - 316nM causes a further decrease in the T-wave amplitude while also suggesting hERG block.
  - At 100 and 316nM, the compound caused a significant lengthening of the FPD and T-wave. 100nM and 316nM Vanoxerine demonstrate safety. Further analysis of the patients in this trial will be warranted to determine possible DC effects. Due to the 34% clearance of Vanoxerine, it is possible that the patients may have been on another drug that was an inhibitor.

Conclusions
- Use of the MEA and CISC derived cardiomyocytes identified a proarrhythmic liability as well as effects on the field potential duration.
- At 100 and 316nM, the compound caused a significant lengthening of the FPD of greater than 40%.
- There was a flattening at the other doses also but they were significantly less. Even 1µM caused a less severe lengthening.
- There is a dose dependent decrease in NA amplitude and slope.
- There was a significant flattening of the T-wave at the top 3 concentrations suggesting hERG block.
- At the 316nM concentration, Vanoxerine caused arrhythmia about after 3 hours in 4 out of 7 wells. 3 hours is a delayed response not usually associated with hERG induced arrhythmia.
- The Cmax for Vanoxerine with a 400mg dose which was used in the clinical trial was ~831. This would be in the range of effect for the in vitro assay.
- Although plasma protein binding is high for Vanoxerine, in the presence of a high affinity target such as hERG, drug would be expected to find the target due to the on/off rate of the molecule. PB/P is not covariant.
- PB/P was done in FBS containing CDI medium and was found to be close to 100% bound.
- With the slow induction of arrhythmia on the cardiomyocytes, the high on/off rate may suggest that the compound would not have been properly screened at high enough levels for the liability. This may have made previous trials for Vanoxerine demonstrate safety. Further analysis of the patients in this trial may be warranted to determine possible DC effects. Due to the 34% clearance of Vanoxerine, it is possible that the patients may have been on another drug that was an inhibitor.