**Effect of ozanimod (RPC1063) on action potential parameters in adult human Purkinje fibers**

**Short title: Ozanimod on Purkinje fiber action potentials**

**N. Abi-Gerges[1],** P. E. Miller[1], A. Ghetti[1], F. L. Scott[2], K. R. Taylor Meadows[2], B. Clemons[2], P. Frohna[2], G. J. Opiteck[2]

[1]AnaBios Corporation, San Diego, California, United States; [2]Receptos, a wholly owned subsidiary of Celgene, San Diego, California, United States

**Background:** Ozanimod (RPC1063), an oral, once-daily immunomodulator that selectively targets sphingosine-1-phosphate receptors $S1P_{R1}$ and $S1P_{R5}$ has shown therapeutic benefit in clinical trials of relapsing multiple sclerosis and ulcerative colitis (Cohen, *Lancet Neurol*, 2016; Sandborn, *NEJM*, 2016). Its effects on cardiac action potential (AP) parameters in a human ex-vivo AP model (Pagel, *J Pharmacol Toxicol Methods*, 2016) were examined.

**Methods:** At pacing rates of 1 and 2 Hz (mimicking normal and elevated heart rates, respectively), human Purkinje fibers (PFs) from female hearts were used to evaluate ozanimod and fingolimod effects on AP duration (APD) at 30, 50, and 90% repolarization (APD30, APD50, and APD90) as well as recognized pro-arrhythmia predictors (triangulation [ADP90 - APD30], short-term variability [STV] of APD90, and incidence of early-after-depolarizations [EAD]). Vehicle control (DMSO 0.3%) and flecainide (10 μM) were used to determine PF stability and responsiveness (positive-control), respectively.

**Results:** Ozanimod, up to 150 nM, had no significant effects on APD or beat escape (BE; electrical stimulus does not trigger an AP after full repolarization) induction, and did not increase the manifestation of pro-arrhythmia markers. Although fingolimod, up to 500 nM concentration, also had no significant effects on APD, triangulation, or EADS, it did increase STV (APD90). Moreover, 50 nM fingolimod showed BE, which was more pronounced at 500 nM, and even more so at 5000 nM, showing clear dose-dependent increases. Furthermore, PAT-1229 ($S1P_{R3}$ antagonist), reversed fingolimod-induced BE. Vehicle controls showed no change in APD, any manifestation of pro-arrhythmic markers, or BE. Flecainide (sodium channel blocker) decreased APD30 and APD50, increased triangulation and STV (APD90) with no induction of EADs, but elicited BE.

**Conclusion:** Unlike fingolimod, ozanimod did not alter any AP parameters, was devoid of pro-arrhythmic potential, and did not alter conduction in ex-vivo human cardiac PFs. This may result from ozanimod's lack of agonism at $S1P_{R3}$.

**Disclosure:** N. Abi-Gerges, Financial support for research: Celgene. P. E. Miller, Financial support for research: Celgene. A. Ghetti, Financial support for research: Celgene. F. L. Scott, Shareholder: Celgene. K. R. Taylor Meadows, Shareholder: Celgene. B. Clemons, Shareholder: Celgene. P. Frohna, Shareholder: Celgene. G. J. Opiteck, Shareholder: Celgene.