BXQ-350 may protect from the direct cytotoxicity of chemotherapeutic agents leading to chemotherapy induced peripheral neuropathy

Background:
Chemotherapy Induced Peripheral Neuropathy (CIPN) is a debilitating side effect associated with many antineoplastic chemotherapeutic agents including cytotoxic and targeted agents. It significantly impacts cancer patients' quality of life during treatment, and may cause lasting neuropathy and shorten treatment regimen, potentially impacting clinical benefit. The pathology of CIPN is complex and still not completely understood. Damages to nerve cells are believed to be directly resulting from the antineoplastic agents' cytotoxicity, and inflammation and the immune system are believed to be involved as well. Evidence suggests that intervention of certain GPCRs (e.g., cannabinoid receptors and others) may be useful as potential treatments. Altered neuronal sphingolipid metabolism has been linked to neuropathic pain and elevated plasma levels of sphingosine-1-phosphate (S1P) have also been associated with patients receiving chemotherapy and developing CIPN; therefore, modulating S1P levels may also be a potential treatment.

Method:
BXQ-350 is a nanovesicle of Saposin C, an allosteric activator of sphingolipid metabolism, that lowers systemic S1P; Saposin C has been reported to activate certain GPCRs, including GPR37. BXQ-350 was investigated in an adult Phase 1 dose-escalation safety study in heavily pretreated all-comer cancer patients with advanced solid malignancies (NCT02859857). The cytoprotective properties of BXQ-350 against multiple agents known to induce CIPN were investigated *in vitro* in neuronal PC12 cells and BXQ-350's CIPN mitigation properties were investigated *in vivo* in a CIPN preclinical model.

Results:
A pancreatic cancer patient with chronic CIPN at time of enrollment in the Phase 1 study spontaneously reported a significant improvement of her neuropathic symptoms shortly after receiving BXQ-350; several patients had similar improvements. Results from preclinical experiments in PC12 cells revealed that BXQ-350 at concentration as low as 50 nM protected cells from oxaliplatin, paclitaxel, bortezomib or MMAE and promoted neurite growth. BXQ-350 was subsequently investigated in a murine oxaliplatin-induced CIPN preclinical model, showing a dose-dependent reduction of thermal and mechanical allodynia correlating with decreasing systemic S1P levels.

Conclusions:
Preclinical results demonstrated that BXQ-350 was highly effective at protecting neuronal cells from antineoplastic agents known to induce CIPN and prevent CIPN in a preclinical model. These results appeared to support the clinical observation that BXQ-350 alleviated CIPN symptoms in several patients soon after receiving BXQ-350. Additional studies are on-going.