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## Evaluation of systemic pan-CLK/DYRK inhibition on organ function and tissue self-renewal

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Proteome diversification through extensive pre-mRNA alternative splicing (AS) is a fundamental aspect of cell fate determination and tissue specialization. The CDC2-like kinases (CLK1-4) and the dual specificity tyrosine phosphorylation regulated kinases (DYRK1-4) have been recognized as participating in signal transduction-dependent alternative splice junction selection through phosphorylation of their substrate proteins- the serine/arginine rich splicing factors (SRSF1-12). The use of CLK/DYRK kinase inhibitors, with various selectivity and potency profiles within the CMGC family, has implicated this regulatory process in both development and disease. Furthermore, an emerging appreciation for the key role of AS in support of tumorigenesis indicates the CLK/DYRK kinases may represent a druggable oncology target class. However, careful evaluation of potential toxicities associated with inhibition of these kinases has not yet been reported. To address this need, the preclinical toxicity profile of SM08502, a potent pan-CLK/DYRK inhibitor, was characterized in multiple exploratory and GLP studies performed in rats and cynomolgus monkeys. Daily dosing of SM08502 was generally well-tolerated in both rats and monkeys, with limited target organ toxicities. Major clinically relevant findings included gastrointestinal (GI), bone marrow and lymphatic organ toxicities in both rats and monkeys. GI toxicity was characterized as villous blunting, single cell necrosis of the epithelium, hemorrhage, inflammation, and edema. These findings in the GI tract manifested clinically as emesis, inappetence, and diarrhea. Microscopic findings suggest a distinct mechanism from cytotoxic agents such as chemotherapy. Morphological evaluation suggests SM08502 primarily affects GI villar epithelial cell dynamics without impairing crypt cell replication or survival. Complete recovery of GI tract findings upon dose holiday was demonstrated in both the rat and the monkey. The SM08502-related hematological findings included decreased reticulocytes, and leukocytes (primarily monocytes and lymphocytes) in both species. These hematological effects contributed to decreased hematopoietic cellularity (all lineages) in the bone marrow and lymphocyte depletion in lymphatic organs (thymus, spleen, lymph nodes and GALT (gut-associated lymphoid tissue)). The nonclinical experience with SM08502 therefore suggests an acceptable safety profile, with adverse events limited to transient reversible GI and hematological findings.

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