Effects of Epacadostat with Co-Administration of Linezolid on Brain Extracellular Fluid Concentrations of Serotonin: An Intracerebral Microdialysis Study in Sprague-Dawley Rats
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Purpose
Epacadostat (EPAC) is a first-in-class and orally active inhibitor of the enzyme indoleamine 2,3-dioxygenase 1 (IDO1). It is currently in multiple clinical trials in combination with checkpoint modulators. Since the substrate for IDO1 is tryptophan (Trp), there is a theoretical concern that inhibition of IDO1 may increase the local pool of Trp and subsequently serotonin. Increased levels of serotonin may lead to serotonin syndrome (SS) when administered alone or in combination with other serotonergic agents, such as monoamine oxidase inhibitor (MAOI). As a precautionary measure, the use of MAO inhibitors such as linezolid, is prohibited with EPAC in clinical trials. The objective of this pre-clinical study was to evaluate the effect of EPAC on brain extracellular fluid concentrations of serotonin in rats, using microdialysis.

Methods
Studies were conducted using microdialysis in rats either alone or with co-administration of linezolid. In addition, linezolid in combination with fluoxetine, a selective serotonin reuptake inhibitor (SSRIs), was used as positive control.

Results
While fluoxetine increased the brain extracellular serotonin levels by 2 – fold vs the vehicle control, this effect was magnified to a 6 – fold increase when fluoxetine was combined with linezolid. In contrast, neither EPAC alone nor in combination with linezolid had an effect on the brain extracellular serotonin levels. In a separate study, it was shown that EPAC does not penetrate the blood-brain barrier (BBB) in rats.

Conclusion
In summary, these microdialysis data as well as the CNS penetration data in rats suggest that SS is unlikely following treatment with either EPAC alone or with combination with MAO inhibitors such as linezolid.