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A proposal for expansion of current guidelines for the genotoxicity testing of new drugs: The case of BIA 10-2474, a novel fatty acid amide hydrolase inhibitor

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The genotoxicity of 3-(1-(cyclohexyl(methyl)carbamoyl)-lH-imidazol-4-yl)pyridine 1-oxide, BIA 10-2474, a novel fatty acid amide hydrolase (FAAH) inhibitor developed by BIAL for treatment of medical conditions in which there is an advantage in enhancing the level of endogenous anandamide (AEA) and tonically increasing the drive of the endocannabinoid system, was evaluated for its genotoxicity. Studies included the Ames (*Salmonella typhimurium*) reverse mutation test, the *Escherichia coli* WP2uvrA test, an in vitro chromosome damage assay in human lymphocytes, and an in vivo micronucleus test in mice. All results were negative. Despite standard comprehensive and meticulous toxicological evaluation, apparent and catastrophic neurotoxicity in the first-in-human phase 1 study in 2016 resulted in cessation of the trial. While the mechanism underlying the adverse events remains ill-defined, there is rationale for expansion of routine ICH harmonized guidelines for preclinical Geno toxicologic testing. We present both a hypothesis for the mechanism of neurotoxicity and a propose a path forward for a more comprehensive evaluation of promising new drugs.

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